SOCIAL SCIENCES

DUPLICATE

BULLETIN ON NARCOTICS

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Bulletin on NARCOTICS

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UNITED NATIONS

DEPARTMENT OF SOCIAL AFFAIRS

New York

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The Surprising Extinction of the Charas Traffic

Charas is the name used in India for the crude resin of Cannabis, the most potent form of the natural drug.

Although much has been written about the necessity of growing Cannabis or "Indian hemp" in a very hot or even a tropical climate if a high yield of resin is to be obtained, in fact charas was never a product of tropical India, but was imported into India from Sinkiang, the westernmost province of China, in Central Asia. The centre of the trade was at Yarkand, which is situated at about 38° North latitude, and charas was produced in this region, formerly known as Chinese Turkistan.

Three types of hemp drugs were used in India: bhang, ganja, and charas.[1] Their use was stated to be largely "quasi-medical", as with opium. Almost all the charas, however, was consumed by smoking, and it is generally considered the worst and most addiction-forming of the hemp drugs. Formerly, the Government of India permitted the import of 70,000 kilogrammes annually. Today, this traffic does not exist. It was voluntarily destroyed by the provincial government of Sinkiang, in furtherance of the aims proclaimed by the Government of China to reduce the world traffic in narcotics used for addiction. This surprising development took place, to a great extent, during the war years and thus it passed almost completely unnoticed by the world at large. In fact, even the Government of China, occupied as it was with the war against the Japanese, and, so far as narcotics were concerned, with the struggle against opium, paid not the slightest attention, after 1935, to events concerning Cannabis in far-distant Sinkiang. The story after that date can only be traced through the annual reports of India.

In 1932, the annual report of China stated: "Certain wild species of hemp were reported to be indigenous in the province of Sinkiang, where the leaves of the plant are sometimes smoked by the aboriginal tribes". In 1933, the report stated: "the result of analysis by the National Health Administration indicated that the wild species of hemp indigenous in the province of Sinkiang and *Cannabis indica* were homogenous. Indian hemp was, after the publication of this result, included in the list of narcotic drugs and hence controlled in strict accordance with the regulations governing narcotic drugs".

In 1934, the annual report of China stated: "since Indian hemp was listed under narcotic drugs, as referred to in the report for 1933, no import certificate nor export permit for this drug was issued by the Chinese Government during the year under review". In 1935, the report stated: "Indian hemp. Only a very small quantity is grown in Sinkiang. (On each leaf, there is a coat of velvet-like substance which is scraped off, mixed with tobacco, and used by the Natives.) In 1934, the Chinese Government issued circular instructions to the provinces and municipalities for the suppression of Indian hemp".

This meagre information, which does not even mention the extensive cultivation in Sinkiang and the legal exportation of thousands of kilogrammes of charas annually to India, is all that can be gleaned from the annual reports of China. It is evident, however, that the prohibition of the export of charas, which was soon mentioned in the annual report of India, was pursuant to instructions of the Government of China of that time, and was undertaken by the Provincial Government of Sinkiang in 1934, although the full effect did not even begin to be felt for several years.

The decision of the Chinese to end this trade was a most surprising one, for not only was this action not requested by the Government of India (at least so far as the record shows), but also the trade was entirely legal under the Conventions, and that for three different reasons:

(1) The 1931 Convention, to which China acceded in 1933, did not control Cannabis (Indian hemp).

(2) China was not a party to the 1925 Convention, the only one which did control Indian hemp and its product, charas.

[1] In the annual report of India for 1949, E/NR.1949/107/Add.2, page 2, the following is stated:

"For all practical purposes, drug addiction in India means smoking of opium, consumption of Indian hemp in the form of charas, and the improper use of manufactured drugs. Oral consumption of opium, and of Indian hemp in the relatively harmless form of bhang, has always been permitted; smoking of Indian hemp in the form of ganja is still permitted in many states. Consumption of charas in India is now negligible. The indigeous hemp plants do not yield any substantial quantity of resin and imported supplies of charas from Central Asia have been stopped for some years. Manufactured drugs are, generally, too expensive to be extensively put to an improper use in India. All indigenous supplies are strictly controlled and there is no evidence to suggest that diversion to illicit use takes place on any substantial scale. Consumption of ganja is still permitted in some states, but all states have now decided progressively to restrict both the consumption of Indian hemp and the oral consumption of opium".

(3) Even if China had been a party to the 1925 Convention or wished to observe its provisions, the relevant provision (article 11, 1 (*a*)) merely required that "the Contracting Parties undertake: (*a*) to prohibit the export of the resin obtained from Indian hemp and the ordinary preparations of which the resin forms the base (such as hashish, esrar, chiras, djamba) *to countries which have prohibited their use,* and, in cases where export is permitted, to require the production of a special import certificate issued by the government of the importing country stating that the importation is approved for the purposes specified in the certificate and that the resin or preparations will not be re-exported". Since the Government of India had not prohibited the use of charas and, in fact, continued to use it as long as it was available, no necessity existed in the Convention to prohibit the trade. The prohibition was, however, in furtherance of the aim of the Government of China, to reduce, as far as possible, the world-traffic in narcotics used for addiction.

In taking up the story from the annual reports of India, it will be best to go back a number of years and see what the situation had been.

For 1923, India reported:

"The use of the hemp drugs is mainly an internal problem, though there is also known to be an illicit market for the drugs in Egypt. The plant grows wild in India and the use of the drugs for their narcotic effect is based upon long tradition that has been traced back as fas as the Vedas. The consumption of the drugs is controlled on lines very similar to those applied to opium. There is no government factory, but cultivation of the plant and the collection of the wild product are governed by the issue of licences. The drugs are stored after collection in government depots and issued to licensed vendors under conditions closely analogous to those under which opium shopkeepers work. The preparations known as bhang and ganja are made from the native product (bhang is the liquid strained off mature leaves and ganja consists of the female flowering tops with the resinous exudation on these). In addition to these two forms, another preparation known as charas is imported from Central Asia (Yarkand). This is a resinous substance which appears upon the leaves, young twigs, bark of the stem and even young fruits of the plant in cold climates. These imports are controlled as closely as the native production, a special warehouse having been established at Leh in which they are deposited and from which they are distributed."

The definition of bhang in the foregoing paragraph was soon changed to refer to the leaves of the plant (*Cannabis sativa*) rather than the beverage which is sometimes prepared from them.[2]

The consumption of charas, in 1923, was reported for "British India" as 1,432 maunds (53,554 kilogrammes). In 1925 only 505 maunds were reported, but figures were not available for the United Provinces and Delhi, where 1,010 maunds had been consumed in 1923. In 1926 the consumption was 58,322 kilogrammes. This seems to have been the first printed report, and the first to give figures for the Indian States. Consumption in the Indian States amounted to 15,445 kilogrammes; thus the total consumption for India was 73,767 kilogrammes.

Besides this large legal consumption, there was a considerable smuggling trade in charas, also originating in Chinese Turkistan. The 1926 annual report stated:

"With a view to stop the smuggling of charas from Central Asia via Chitral, a warehouse has been established at Chitral and the preventive staff on the North West Frontier Province has been strengthened."

In 1927 the consumption in British India was 43,595 kilogrammes, in 1928 it was 45,995 kilogrammes, and 56,510 kilogrammes in 1929.

The annual report for 1928 stated:

"The Government of India consulted the local governments as regards the desirability and practicability of prohibiting the import, possession and sale of charas in India, and their views were awaited. With a view to suppressing the wholesale illicit import of the drug into India, duty thereon has been reduced from Rs. 60 to Rs. 20 per seer in the Punjab, Baluchistan, the North West Frontier Province and Delhi. The Excise Staff in Baluchistan was also strengthened, with a view to exercising more effective control over the smuggling of opium and charas from across the foreign territories."

The annual report for 1930 gave the following information about the hemp drugs:

"The narcotic products of the hemp plant used in India are ganja, charas and bhang. Ganja and bhang are eaten as well as drunk. The former is also smoked. Charas, if medicinal uses be excepted, is almost always smoked. The simplest method of consuming ganja and bhang is to pound them with certain spices, and then swallow the paste in the form of a bolus. The green leaves of the plant are not usually chewed anywhere. Ganja and bhang are also consumed in the form of sweetmeats."

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[2] In the annual report of India for 1949, E/NR.1949/107/Add.2, page 11, the following is stated:

"Ganja includes the dry flowering tops of the female plant which have become coated with resin. This form is usually consumed by smoking in a country-made pipe. Bhang denotes the leaves and flowering shoots, whether green or dried, generally prepared for consumption by pounding with sugar and spices to produce an ingredient of drinks or sweetmeats"

This report also mentioned the fact that "despite the vigorous efforts of the Excise and Police Departments, some smuggling of contraband charas from Chinese Turkistan (via Chitral) continues". Consumption amounted to 58,475 kilogrammes. This report also gave figures for imports:

"The only preparation of the hemp plant imported from abroad is charas. It is imported from Central Asia (Yarkand), under a transport-in-bond pass granted by the British Joint Commissioner at Leh, by persons licensed by the Punjab Government. Charas is also imported from Central Asia via Chitral. The quantity of the drug imported into the Punjab from the charas warehouse at Ley during the calendar year 1930 was 1,976 maunds 27½ seers. Besides this quantity, 334 maunds 17 seers were imported in bond from Chitral into Punjab, and 134 maunds 13 seers into Peshawar (North West Frontier Province)."

The total imports were therefore 91,471 kilogrammes of charas.

In 1931 the total imports were 97,949 kilogrammes, while reported consumption in British India was 52,458 kilogrammes and in the Indian States 15,084 kilogrammes; total consumption, 67,542 kilogrammes.

In 1932, apparently the last report to state the imports, they were given as 1,668 maunds 16 seers—a drop to 62,380 kilogrammes imported. The consumption in British India was 51,721 kilogrammes.

The annual report for 1932 had this to say about the smuggling problem and the illegal traffic:

"There is a considerable amount of smuggling of charas across the Peshawar border and through the Kohat Pass. Smuggling of charas from Chinese Turkestan constitutes a serious problem and the only effective means of suppressing the traffic appears to be the assumption of complete control over the production of charas by the Chinese authorities."

The annual report for 1933 added:

"Charas smuggling in the Central Provinces continued unabated, Nagpur and Jubbulpore being the chief centres of consumption and distribution to other districts. The Punjab Government is still maintaining a special staff of excise officials in order to intercept the passage of charas from Afghanistan and the North West Frontier Province towards the United Provinces and other adjacent parts of India."

Consumption in British India, in 1933, was 53,732 kilogrammes, and in the Indian States 20,488 kilogrammes: total consumption, 74,220 kilogrammes.

The foregoing reviews the situation up to the eve of the decision by the Chinese authorities to end the traffic, licit as well as illicit. As will be remembered, this apparently took place in 1934.

The annual report of India for 1934 had a great deal to say about charas smuggling. The following was given in the chapter on illicit traffic:

"Charas, cocaine and opium are the principal articles of smuggling. Charas is smuggled into India from across the Peshawar border by trans-border Pathans or through the Tribal Territory in Kohat Pass. The drug is obtained by the traffickers from Kashgar in Chinese Turkistan. Distribution of illicit charas is centred in Bajaur (Tribal Territory) whither it is conveyed from Chinese Turkistan through Afghan territory. The smuggling of charas for consumption in the Punjab has considerably decreased since the reduction in duty to Rs. 20 a seer. The illicit through traffic in charas, however, still continues unabated. The imports of contraband charas into the North West Frontier Province appear to have decreased during the year. This is presumably due to the disturbances in Central Asia. But it is believed that stocks of illicit charas are still abundant in the vicinity of the external border of British India.

"Inter-provincial smuggling. The prohibition of charas consumption in certain areas and large variations in duty on charas in various provinces have stimulated inter-provincial smuggling of charas. Local governments are taking action in the matter by strengthening their preventive staffs or by allowing the use of the drug or by reducing the rate of duty on the drug. In order to discourage charas smuggling, two charas shops have been opened in the Central Provinces, one at Nagpur and one at Jubbulpore, from 1 January 1935, after the prohibition of the drug had been maintained for a period of about 9½ years.

"((Illicit) charas is usually adulterated with foreign matter to the extent of about 20 to 25 per cent. Tobacco and catechu are frequently added to charas and opium, respectively, to increase the weight.)"

The illicit charas sold at Rs. 10 to 120 per seer wholesale, Rs. 26 to 300 per seer retail.

In other parts of the annual report for 1934 there was some further discussion of the smuggling:

"Smuggling of charas from Chinese Turkistan (though slightly slackened in the latter half of 1934 owing to the disturbed conditions prevailing in the tract between Chitral and Yarkand)... constitutes a serious problem and unless stricter control is exercised over the production of drugs in those areas it is difficult to suppress illicit traffic in them... Most of the charas stocks that had been held up by the smugglers in the Khyber and Kohat Passes owing to the preventive measures adopted by the Government of the North West Frontier Province, deteriorated by lapse of time, and information was

received in the N.W.F.P. Excise Intelligence Bureau that the Tribal Territory smugglers had mixed fat, linseed oil and fresh leaves of bhang with their old stocks of charas so as to make it marketable by restoring its smell and oily greenish appearance. The illicit charas recovered recently in many cases was found to be of inferior quality."

The consumption of charas in 1934, in British India, was 55,128 kilogrammes, and a stock of 3,286 kilogrammes was reported. The consumption in the Indian States was 27,865 kilogrammes: total consumption 82,993 kilogrammes.

In the annual report for 1935 it was stated under "International Co-operation":

"The traffic in contraband charas has somewhat declined owing to the prohibition of its export from Chinese Turkistan."

However, aside from this one sentence, there was nothing in the report to show any decline in the traffic. New rules were set up to control it, consumption remained at about the same level as before, and smuggling continued.

"The Central Charas (Import by Land) Rules, 1935, made under Section 7 (2) of the Dangerous Drugs Act, 1930, were finally notified and brought into force from 1 October 1935. The object and scope of these rules is to control the import of charas by land into British India. They supersede regulations which were made under local laws before the passing of the Dangerous Drugs Act. The import can be effected only by certain prescribed routes and also under authorizations granted by officers empowered in this behalf."

"*Central Provinces.* The sale of charas, which had been forbidden since 1925, was once more licensed and the limit of individual possession was fixed at half a tola. The reason for once more legalizing the sale of charas in the Central Provinces was the considerable increase in offences of smuggling of the drug into this province since the year 1930."

"*North West Frontier Province.* In order to check the smuggling of charas, fifteen excise detectives were engaged with effect from 1 April 1935—as an experimental measure for one year—with satisfactory results."

The consumption was 50,342 kilogrammes in British India, and a stock of 8,576 kilogrammes was reported. The consumption in the Indian States was 22,041 kilogrammes: total consumption 72,383 kilogrammes.

The chapter of the annual report for 1935 on illicit traffic mentioned that, for the first time, "the garda charas, which was of inferior quality, was also smuggled from Gardez, in Afghanistan".

The annual report for 1936 stated:

"The Chinese authorities announced their intention to prohibit the cultivation in and export from Yarkand of charas. The Punjab Government had therefore to take special steps to control the issue of charas from their bonded warehouses to other provinces and Indian States. It was decided to issue charas to all consuming areas including the Punjab on the basis of the average monthly consumption during 1934-35. For the Patiala, Nabha and Sind states the supplies were based on the average monthly consumption of 1932-33."

The significance of the announcement of the Chinese authorities in 1936 is not entirely clear. Perhaps the prohibition of cultivation was carried out in stages. It was still a few years before this prohibition had any effect on the licit consumption in India. If the prohibition was not carried out by degrees, it is a mystery where all the supplies of charas were coming from, as no large stocks were reported.

The annual report of India for 1936 also stated: "The imports of contraband charas into the Punjab and the North West Frontier Province have diminished to a great extent on account of the prohibition imposed by the Chinese Government on cultivation of hemp plant in Central Asia and export of charas".

Consumption in British India was still 51,884 kilogrammes and the stock was 7,991 kilogrammes. Consumption in the Indian States was 20,799 kilogrammes; thus the total consumption in India, in 1936, was 72,683 kilogrammes.

In 1937 conditions continued to be much the same. The stock of charas in British India at the end of the year was 30,367 kilogrammes. Consumption in British India was 59,800 kilogrammes, in the Indian States 22,254 kilogrammes, total 82,054 kilogrammes. Illicit charas was priced at Rs. 20 to 80 per seer wholesale, Rs. 30 to 180 per seer retail.

By 1938 the supply of charas available to the illicit traffic had nearly ceased. The annual report stated: "The smuggling of charas from Central Asia has largely ceased owing to the prohibition imposed by the Chinese Government, but its illegal import continued out of the stocks of charas previously stored by smugglers of Tribal Territory". Another part of the report stated, however, that "trade in charas on a large scale has ceased and smugglers have diverted their attention towards illicit traffic in opium which is smuggled from Afghanistan and the adjoining trans-Indian Tribal Territory". Illicit charas was priced at Rs. 25 to 100 per seer wholesale, Rs. 50 to 240 per seer retail.

The stock of charas in British India was 808 kilogrammes. Consumption in British India was 50,431 kilogrammes, in the Indian States 19,835 kilogrammes: total consumption, 70,266 kilogrammes for 1938.

In 1939, for the first time, the licit consumption of charas was substantially affected by the shortage of supply. There was, however, still some smuggling. Under "Inter-provincial smuggling" the annual report stated, "the smuggling of charas from the North West Frontier Province and the Punjab received a set-back, partly as a result of difficulties in obtaining supplies from Chinese Turkistan, which is the main source of supply. The prohibition of charas consumption in certain provinces and the disparity in the prices prevailing in the Punjab and other provinces still make smuggling attractive. An increase in the duty on charas in the United Provinces and its total prohibition in the Central Provinces led to the smuggling of charas from the Indian States and the North West Frontier Province to these provinces". Prices had apparently not risen to any great extent; they were Rs. 30 to 150 per seer wholesale, Rs. 40 to 240 per seer retail.

The stock in British India at the end of the year was 3,798 kilogrammes. The consumption in British India was 33,884 kilogrammes, in the Indian States 14,024 kilogrammes: total consumption, 47,908 kilogrammes.

For 1940, the annual report stated, "the trade in contraband charas has almost entirely ceased owing to the prohibition of its export from Chinese Turkistan". The licit consumption in British India was now down to 25,582 kilogrammes.

The stock in British India was 6,164 kilogrammes. Reported consumption in the Indian States was up a little from the year before, to 15,367 kilogrammes: total consumption for India, 40,949 kilogrammes.

The annual report for the Indian States, consolidated for the years 1938, 1939, and 1940, included the following note:

> "*Charas.* This drug was not much in demand and whatever quantity was consumed was obtained mostly from the warehouses in British India. The question of manufacturing the drug in Kashmir State, on account of the prohibition imposed by the Chinese Government on exports from Yarkand, was under consideration of the State Government during the year 1940."

The annual report for the Indian States for 1941 stated that manufacture of charas was under the consideration of the State Government of Kashmir during 1941 also. Consumption in British India was now down to 22,473 kilogrammes, but in the Indian States it was up to 18,203 kilogrammes: total consumption, 40,676 kilogrammes. The stock in British India at the end of 1941 was 4,683 kilogrammes.

The annual report for 1941 had the following to say concerning smuggling: "There was no smuggling of fresh illicit charas. A few cases of smuggling of garda charas of inferior quality from the Tribal Territory were detected during the year". A little inter-provincial smuggling continued from existing stocks. Prices apparently were not up to any extent—Rs. 35 to 130 per seer wholesale, Rs. 60 to 400 per seer retail—but the illicit charas was more than ever adulterated. "Charas was usually mixed with bhang made into paste to the extent of 50 per cent."

The annual report for 1942 had a number of interesting items. First concerning the illicit traffic:

> "The illicit import of charas has practically ceased, though a few cases of smuggling of garda charas (which is of inferior quality) from Tribal Territory into the North West Frontier Province were detected during the year.
>
> "Small but heavily adulterated quantities (of charas) are reported to be coming from the Afghan border... Tobacco, catechu, bhang, honey, (are the chief adulterating ingredients used) in the case of charas.
>
> "The illicit import of ganja from Nepal continues and is on the increase on account of its cheapness. Charas not being available the smugglers have directed their attention more towards ganja."

Under "Raw materials" (i.e., in regard to the licit charas) it was stated, "Supplies of the drug have now ceased". Under "Administration": "Owing to stoppage of supplies from Central Asia, little charas was available during the year and as a result certain addicts have taken to opium and ganja".

The stock of charas in British India was 2,717 kilogrammes at the end of the year. The consumption was 11,891 kilogrammes in British India, 8,145 kilogrammes in the Indian States: total consumption 20,036 kilogrammes.

The report for the Indian States contained the statement: "*Charas.* Since the stoppage of supply of this drug from Central Asia the demand for the drug has gone down and whatever quantity was required for consumption was obtained from warehouses in British India".

The 1943 annual report contained much the same information on illicit traffic as that of 1942. Illicit prices were given as Rs. 25 to 250 per seer wholesale and Rs. 65 to 360 per seer retail and were said to be generally a little higher. Legitimate charas consumption was now down to 2,924 kilogrammes in British India, but ganja consumption had gone up from 151,225 kilogrammes in the preceding year to 212,764 kilogrammes, an increase of 61,539 kilogrammes; and bhang consumption had gone up from 274,414 kilogrammes in the preceding year to 343,657 kilogrammes, an increase of 69,243 kilogrammes. These were the first great increases since 1937 for either ganja or bhang, although the decline of charas consumption in British India had begun in 1939. As regards the quantities, it will be realized that ganja

is less potent than charas and bhang very much less.[3] The stock of charas at the end of 1943 was 280 kilogrammes.

For 1944, the annual report stated: "Illicit import of charas from Chinese Turkistan has also completely stopped, on account of the reported stoppage of its production there. Garda charas (charas of an inferior quality) however continued to be smuggled, on a fairly extensive scale, into the North West Frontier Province and Baluchistan from Afghanistan and Tribal Territory where it is produced or stored after having been brought from the place of production, *viz*, Gardez in Afghanistan." The prices were said to be Rs. 75 to 350 per seer wholesale, Rs. 90 to 735 per seer retail.

The consumption of charas in British India was now only 565 kilogrammes and the stock at the close of the year was 105 kilogrammes. The consumption of ganja decreased just a little from the preceding year, but that of bhang again increased greatly to 439,216 kilogrammes, an increase of more than 100,000 kilogrammes.

The last year of licit consumption of charas, in India, was 1945. In fact the consumption was only 49 kilogrammes and the stock at the end of the year was nil. Ganja consumption had apparently about levelled off, but bhang consumption again showed a large increase, to 524,377 kilogrammes.

Under "Illicit traffic" the annual report for 1945 mentioned: "*Garda charas*. This inferior quality of charas is prepared by various artificial means from the hemp plant growing wild in mountainous regions... Cases of smuggling (it) into the North West Frontier Province and Baluchistan from Gardez in Afghanistan were quite common during the year. Some Nepali charas was also illicitly imported from the United Provinces."

[3] See footnote on page 1.

In 1946 there was no longer any licit consumption of charas in British India, and the consumption of bhang dropped to about that of 1944, while the consumption of ganja remained nearly the same.

Charas consumption lingered a little longer in some of the Indian States. In 1946 it was only 146 kilogrammes; in 1947 it was 76 kilogrammes but 54 kilogrammes of this was produced locally in Indore State The production of charas in the Indian States was prohibited, and in 1948 the consumption was completely negligible.

The traffic in charas was extinct.

The following table shows the consumption of charas, ganja, and bhang in British India from 1934 to 1946; the decline of charas from 1938 to 1946; and the rise in consumption of ganja and bhang towards the end of that period.

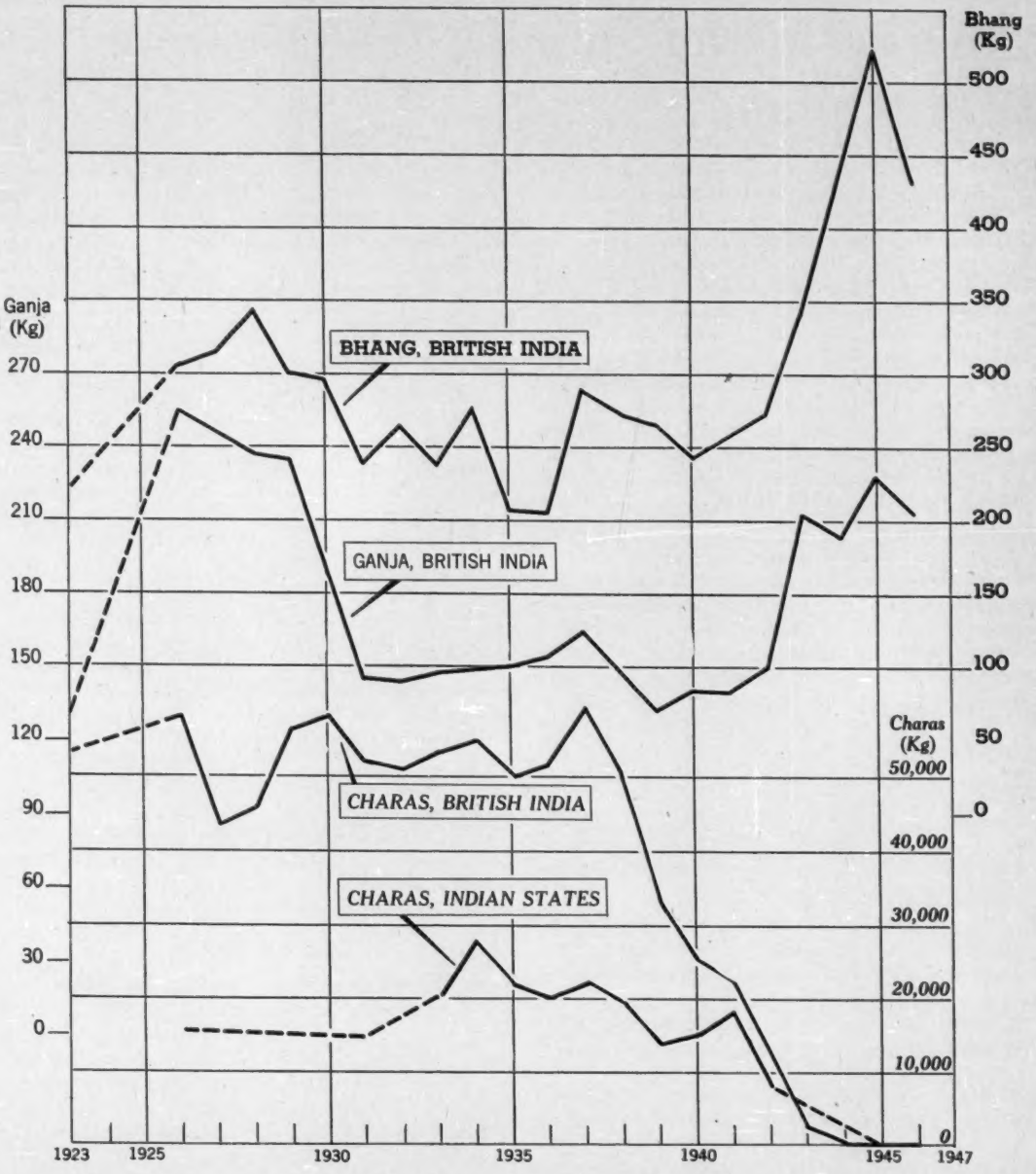
CONSUMPTION IN BRITISH INDIA

In kilogrammes

	Charas	*Ganja*	*Bhang*
1934.....	55,128	150,381	279,146
1935.....	50,342	150,680	207,950
1936.....	51,884	155,083	206,967
1937.....	59,800	165,752	291,637
1938.....	50,431	147,897	274,841
1939.....	33,884	133,056	253,986
1940.....	25,582	141,882	244,603
1941.....	22,473	140,948	260,047
1942.....	11,891	151,225	274,414
1943.....	2,924	212,764	343,657
1944.....	565	203,684	439,216
1945.....	49	228,847	524,377
1946.....	0	214,660	433,630

India and Pakistan became independent in 1947, and both prohibit traffic in charas. There is still a little inferior charas smuggled into India from Afghanistan and Nepal, but it seems fair to say that the great charas traffic is now extinct.

Consumption of bhang and ganja in British India, and of charas in British India and in the Indian States, 1923-1947



(*Note:* the graphs for bhang and ganja are not on the same scale as those for charas, nor do they have the same zero point. The scales are such that 50,000 kg. for charas corresponds to 150,000 kg. for ganja and 250,000 kg. for bhang. In order, however, to separate the graphs, the zero points for ganja and bhang are raised above that for charas. Thus the graphs for bhang and ganja chiefly indicate their relative rise and fall as compared to charas.)

Progress in Determining the Origin of Illicit Opium

The Problem and the Research Programme

Vital as opium and its alkaloids are as medicines, there is certainly even more opium produced and consumed for non-medical purposes, or to put it bluntly, for drug addiction. No one knows the total amount, but it is certainly hundreds of tons, possibly even thousands of tons, over the whole world in the course of a year. Most of the non-medical consumption is in certain producing countries such as China and Iran, but much opium is also smuggled to non-producing countries. Moreover, illicit opium is the main source of illicit morphine and heroine. Sometimes it is converted to the "white drugs" in the country of origin, sometimes only after being smuggled to other countries.

When illicit opium is seized by enforcement authorities, it is often desirable to know from where it came. The circumstances of the seizure may tell something: such things as the port at which a vessel last called, or wrappings of newspapers, poppy leaves, or oiled paper, may be indications. On the other hand, such evidence may be lacking or unconvincing as concerns the origin. An expert may be able to tell the origin by the appearance of the opium itself, its colour and texture. Still better, scientific means may be applied and the opium may be made to disclose its origin by its own nature. This last possibility was discussed at intervals by enforcement officers for some fifteen or twenty years before a comprehensive programme was started to see just what could be worked out.

At the end of the war, and as part of the new United Nations Organization, the Commission on Narcotic Drugs came into being, replacing the Opium Advisory Committee, which had functioned under the League of Nations. The representatives of fifteen governments on the Commission agreed that a scientific assault should be made upon the problem of identifying the origin of seized opium. At its third and fourth sessions, the Commission proposed resolutions 159 II C (VII) and 246 F (IX). These were adopted by the Economic and Social Council on 3 August 1948 and 6 July 1949, respectively.

Under these resolutions an international research programme has been gradually organized, concerned primarily with the development of methods for determining the origin of opium by scientific means. Interrelated topics of special importance such as the study of methods of assay of opium for morphine and codeine contents, are given particular attention. Studies are made both by chemists of the United Nations Secretariat, and by other scientists designated by governments throughout the world.

The producing countries have co-operated in supplying opium of known origin for study. Samples of their own production have been received from China, Greece, India, Iran, Korea, Laos and Vietnam, Turkey, and Yugoslavia; and other samples, not directly from producing countries, have been contributed by France and the United States. From these supplies, samples have been distributed for research in various countries, and scientists are collaborating in Austria, Canada, China (Taiwan), Denmark, United Kingdom, France, Germany, Greece, India, Israel, Japan, Netherlands, Norway, Sweden, Turkey, and the United States of America.

A new series of United Nations documents has been established, dealing with "The Assay, Characteristics, Composition, and Origin of Opium". Twelve papers have thus far been issued in this "Series K" numbered ST/SOA/SER.K/1 to ST/SOA/SER.K/12. In this series, and a few preceding papers, there have been contributions from the United Nations Secretariat and from scientists in Austria, Canada, Turkey, and the United Kingdom. Other scientists are hard at work to learn more about opium in the continuous struggle to suppress the evils of illicit narcotics and at the same time to learn more about the alkaloidal value of different kinds of opium, and to improve control over its legitimate use.

All this co-operation is very valuable in itself. It shows that most of the countries of the world do want to work together. In this particular case, scientists interested in opium and those connected with narcotics enforcement in various countries are working on a common project. As one result of all the discussion, governments become more conscious of the need for controlling opium.

Thus, the opium research would be of real value even if it were finally decided that, as a means of determining origin, the scientific tests would not work.

A story is told about the American inventor Edison. Once an assistant became discouraged over the many experiments on a certain project, 214 or some such

number, made, as he said, "with no success". But Edison said the experiments had been successful because: "We now know 214 things that will not work".

However, there is every reason to believe that the opium research will be completely successful in the positive sense: the methods will work. Recent results obtained by the Secretariat chemists are very convincing on this point, as will be explained.

It may be well to emphasize that the opium research is not an effort to pin transgression on one particular country, but to ensure that all producing countries are conscious of the problem that their opium creates in other countries, and made aware that when any considerable amount of opium is allowed to leak into international illicit traffic, its national origin may be demonstrated by convincing scientific tests. The leading producing countries are themselves co-operating in the United Nations programme, and share in the progress of research.

Recent Results

Codeine

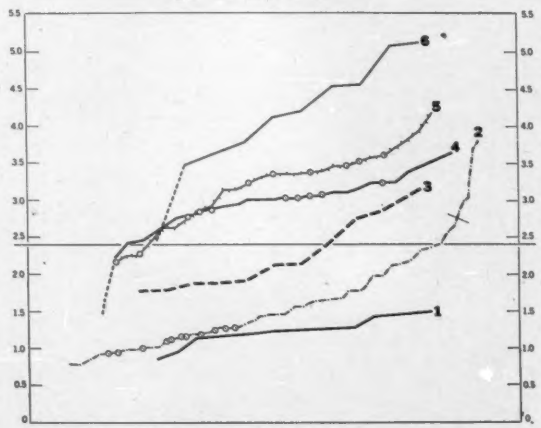
The Secretariat chemists have recently completed a survey of the codeine contents of available samples.

Before the opium research programme ever began, it was well known, from commercial sources, that opium from India and Iran has about twice the codeine content of opium from Yugoslavia and Turkey.

Chart 1 shows curves for the codeine content of opium in different regions. The codeine percentages, according to the United Nations analyses, are taken as ordinates. The values for each region are put in numerical order and then represented as a "curve". As can be easily seen, the codeine percentages are lowest for the region of Macedonia (Yugoslavia and Greece) and are three or four times as high for the Far East (China, Korea, and Mongolia).

CHART 1

Curves of codeine percentages for six opium-producing regions



1. Greece and Yugoslavia (16 samples)
2. Turkey (85 samples)
3. Laos and Vietnam (11 samples)
4. India (29 samples)
5. Iran (27 samples)
6. China, Korea, Mongolia (10 samples)

Ordinates are the percentages of codeine.

The circles on the curves for Turkey, India, and Iran indicate the positions of export samples from these countries. The Turkish export opium is a mixture of all the opium of the country, and the position of the export samples, all on the lower half of the curve, indicates that the Turkish samples higher in codeine are over-represented in proportion to quantity of production in the United Nations collection. Actually the bulk of Turkish production, called "druggist" opium, is very similar to the opium produced in Yugoslavia and Greece. The resemblance has an interesting history. The modern culture of the opium was introduced into Macedonia in the last century, when the region was in the possession of Turkey, but the "druggist" variety of opium is said to have originated, or been developed, in this European region, and was then introduced back into Asiatic Turkey.

It will be noted that the curve for Turkey rises rapidly near the end. However, most of these high to very high samples—including all of those above the cross line on the curve—come from certain districts of Turkey: Malatya and Zile. In subsequent charts, the samples from Malatya and Zile are separated from those from the rest of Turkey, as they belong to an entirely different type of opium.

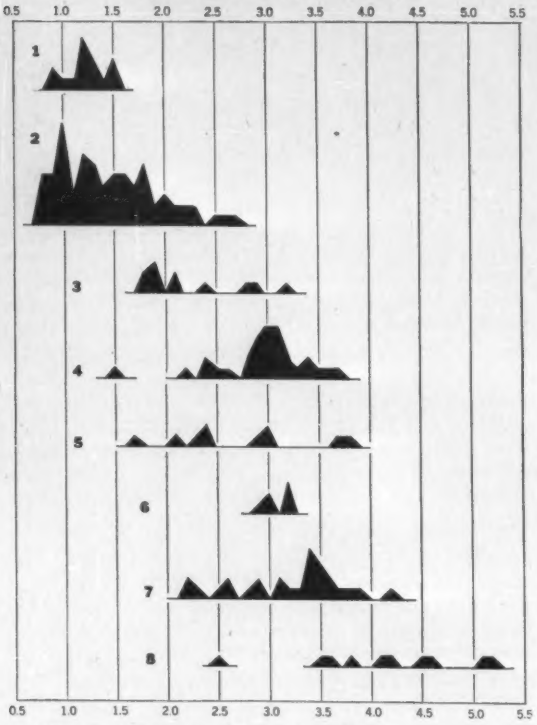
It will be noted that, on the whole, the three lower curves bend upward while the three upper curves bend downward. The significance is that the less usual samples of the lower curves are the ones highest in codeine, causing the curve to rise more steeply at the end (particularly in the case of Turkey); while the less usual samples of the upper curves are those lowest in codeine, so that the curve rises most rapidly at the beginning, and then more or less levels off in a high range. The beginnings of curves 4 and 6 are represented by broken lines, because the first sample in each case is not at all characteristic.

A line at 2.4 per cent separates fairly well the curves for Macedonia and Turkey from those for India and Iran. The curve for the Indochina region is intermediate, but on the whole corresponds to the upper part of the curve for Turkey. Another line at 3.6 per cent separates the high curve for China, Korea, Mongolia fairly well from the curves for other regions, but quite a number of Iranian samples are not much under this value.

Chart 2 shows more clearly the distribution of the codeine groups. Here the codeine percentages are represented as abscissae. In this chart, each sample is taken at the nearest tenth of a per cent of codeine;

CHART 2

Distribution of the codeine groups for eight opium-producing regions



1. Greece and Yugoslavia
2. Turkey, excluding Malatya and Zile
3. Laos and Vietnam
4. India
5. Turkey, Malatya and Zile only
6. Afghanistan
7. Iran
8. China, Korea, Mongolia

Abscissae are the codeine percentages (taken to the nearest tenth).

Ordinates for each curve separately are the number of samples at the particular percentage.

and the ordinates, for each curve separately, represent the number of samples in the United Nations collection at the different values. The peaks, at about 1.2 per cent for Greece and Yugoslavia, between 0.8 and 1.8 per cent for Turkey, but at about 3.0 to 3.1 per cent for India, 3.4 per cent for Iran, are very clearly marked.

Chart 3 shows still another way of representing the codeine data; one which shows most clearly the clustering of samples about certain preferred values, and the more or less definite boundaries for groups. Here the codeine values are again ordinates, and each sample is represented by a separate spot, placed as close to the vertical line used for the particular region, as is possible without overlapping. Eight regions are represented, and one sees that the values for region 1 (Greece and Yugoslavia) are all well under 2 per cent, whereas the values for regions 4 to 8 have hardly started at this figure. Again the values for normal Turkish opium are all through at 3 per cent (only a few samples from the Malatya-Zile region, which is shown separately, are higher), whereas the samples from China, Korea, Mongolia, with only one exception, are well above this value.

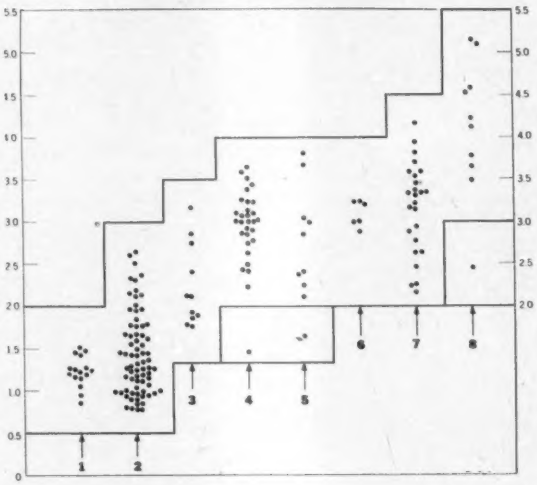
This type of presentation has the most value in connexion with the codeine analysis of seized opium. Having found a value for the seizure sample, it can easily be seen what clusterings are in line with it, and what other groups might be regarded as possibilities. Other tests can then be applied to differentiate between regions that are possible, or most probable, on the basis of the codeine classification.

Codeine—porphyroxine charts

The comparative colorimetric values for the alkaloid "porphyroxine-meconidine" constitute another valuable

CHART 3

Distribution of the codeine percentages of opium for eight producing regions



1. Greece and Yugoslavia
2. Turkey, excluding Malatya and Zile
3. Laos and Vietnam
4. India
5. Turkey, Malatya and Zile only
6. Afghanistan
7. Iran
8. China, Korea, Mongolia

Ordinates are the codeine percentages.

For each sample a spot is placed at the correct height for the codeine percentage according to the laboratory determination, and as close as possible, without overlapping, to the vertical line for the particular region.

means of determining the origin of opium. This very minor alkaloid varies significantly in the different kinds of opium. The porphyroxine values (as they will be called, for short, in this paper) are based on reading the red colour, which the alkaloid yields on heating in dilute mineral acid, in the Lovibond tintometer under certain standard conditions. The values are not percentages but constitute a comparative colorimetric determination.

A chart for the curves of porphyroxine values was given in "The Story of 'Porphyroxine-Meconidine'" *Bulletin on Narcotics*, volume IV, number 1. It corresponds to chart 1 for codeine, and looks rather similar, but the order of the countries or regions is different, Iran being the lowest.

The really interesting and important facts are brought out when the codeine percentages and porphyroxine values are considered together. The charts combining codeine percentages and porphyroxine values throw a strong new light on the problem of determining the origin.

In all the following charts a position is marked for each sample, considered according to its codeine percentage and its porphyroxine value, using the codeine percentage as ordinates and the porphyroxine values as abscissae. All these charts are on the same scale.

Chart 4 shows the positions of the *export samples* of India, Iran, Turkey, and Yugoslavia. It is seen that the export samples from Turkey and Yugoslavia come in exactly the same areas on the chart, but those from India and Iran form two other areas, entirely separate and distinct.

Charts 5 to 8 show all the available samples from China, Korea, and Mongolia (chart 5), India (chart 6), Iran (chart 7), and Turkey (chart 8), with the exception only of a few samples that were found to be adulterated or so substandard that they could not be compared with normal samples. It is easily seen that, in each case, the position of the samples on the chart is different and characteristic. The boundary lines are of course not absolute, but merely direct the eye to the area occupied by the scattered samples.

It is enlightening to superimpose each chart on the others, in turn. It will be found that while there is some overlapping of the indicated areas, in no case does the main clustering of samples for one area fall within the boundary of another one of these areas.

On chart 8 it is seen that Malatya and Zile, in Turkey, have to be treated as a separate producing region from the rest of Turkey, so far as the samples in the United Nations collection are concerned. Some samples from Malatya and Zile are rather scattered on the chart, but the characteristic group is quite obviously at the far right of the chart (highest porphyroxine values) and with codeine between 2 and 4 per cent, whereas the main clustering of the samples of the usual Turkish opium is near the lower left-hand corner of the chart.

▼ Afghanistan
⊗ China, Korea and Mongolia
○ Greece
△ India
● Iran
+ Laos and Vietnam
o Turkey (excluding Malatya and Zile)
▽ Turkey (Malatya and Zile only)
⊕ Yugoslavia

Ordinates: Codeine percentages
Abcissae: Porphyroxine values

CHART 4

Codeine – porphyroxine values for samples of export opium from India, Iran, Turkey and Yugoslavia

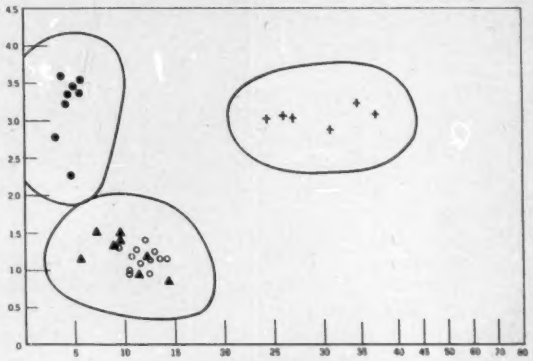


CHART 5

Codeine – porphyroxine values for opium samples from China, Korea, Mongolia

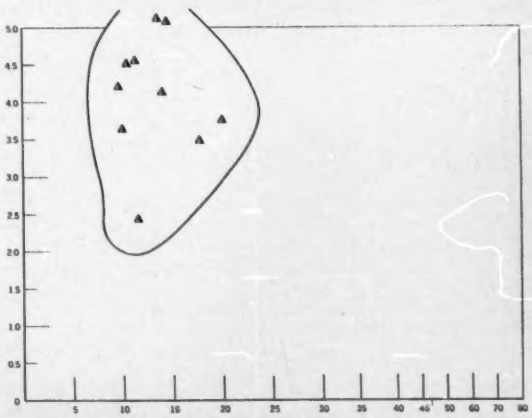


CHART 6

Codeine – porphyroxine values for opium samples from India

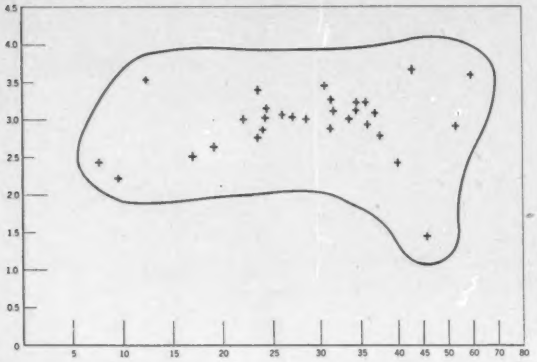


CHART 7

Codeine – porphyroxine values for opium samples from Iran

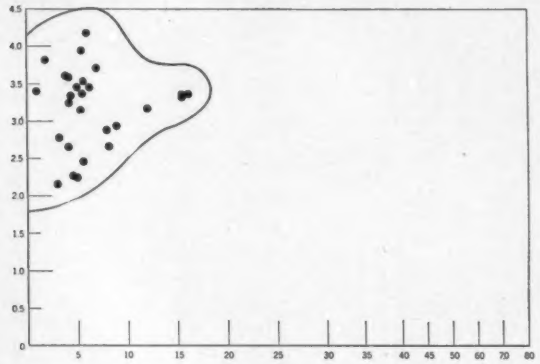


CHART 8

Codeine – porphyroxine values for opium samples from Turkey

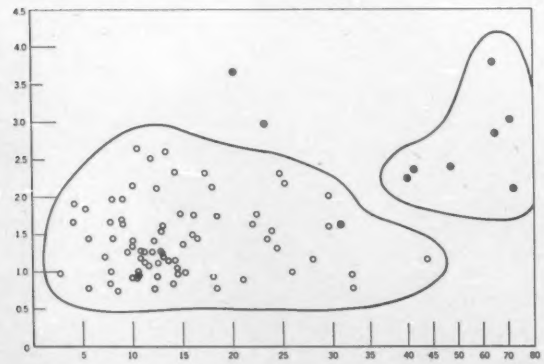


CHART 9

Codeine – porphyroxine values for opium samples from three producing regions: Afghanistan, Laos and Vietnam, Yugoslavia and Greece

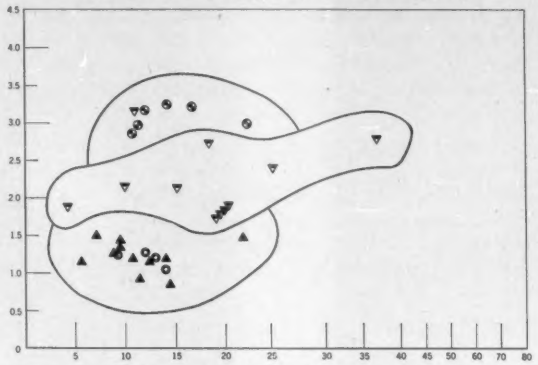


CHART 10

Codeine – porphyroxine values for opium samples from five main producing regions: China, Korea, Mongolia, India, Iran, Turkey, excluding Zile and Malatya; Turkey, Zile and Malatya only

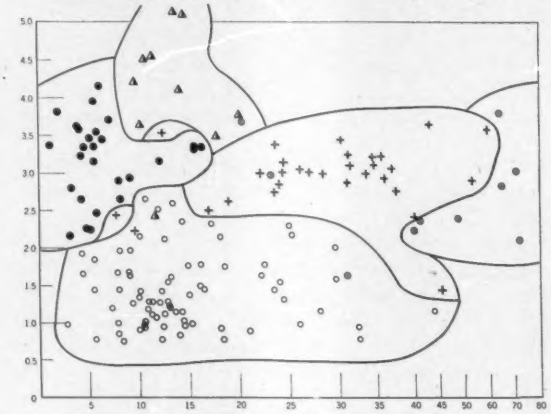
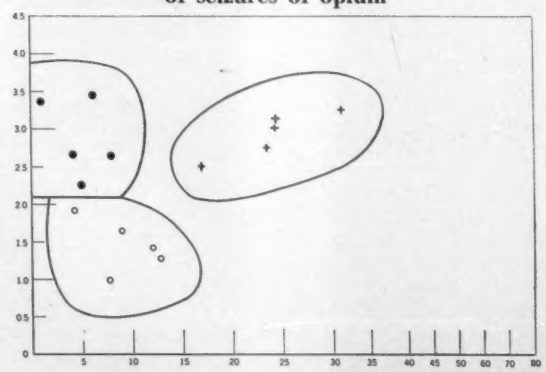


CHART 11

Codeine – porphyroxine values for fifteen samples of seizures of opium



On looking at chart 8, one may have the impression that the Turkish samples spread over nearly all of it, but if it is superimposed on charts 5, 6, and 7, it will be found that the main clustering of the other samples is well outside the Turkish areas and that the samples are not interspersed with each other to any significant degree.

Chart 9 shows three other producing regions represented all on one chart: Afghanistan, Indochina (Laos and Vietnam), and the Macedonian region of Yugoslavia and Greece. Only one sample is represented as "out of place", otherwise definitely separate areas on the chart can be assigned to the three distinct producing regions.

In chart 10 all the samples from the five main producing regions of charts 5 to 8 are represented on one chart. The boundaries now are rather arbitrary, but they show to what a great degree it is possible to draw dividing lines which clearly separate the samples from different regions, and yet have very few samples represented in the "wrong" area. If there were any real interspersion of samples, this would not be possible. The close relation of codeine and porphyroxine values to the origins of the opium is dramatically shown by this chart.

Use of the charts with seizure samples

If the co-ordinates—codeine percentage and porphyroxine value—are determined for a sample of seized opium, its position on chart 10, or on any of the other charts, can be easily noted. If it falls in an area of clustering of samples of a particular region, then (of course taking into account the general appearance of the opium and any known circumstances of the seizure) the origin of the opium may well be perfectly clear. Even if the position of a seizure sample on the chart is on or near a boundary line, or in an area where the various charts show that overlapping occurs, the possibilities as shown by the chart will be quite limited, and when the circumstances of the seizure are taken into account the origin may be determined.

Furthermore, additional tests are already in use, and still others are being studied, to decide the question whenever any doubt may still remain. The most important tests already in use are the microscopical examination with the polarizing microscope, and the morphine determination. The microscopic test will ordinarily distinguish clearly between the opium of Turkey and that of India, or of Iran. The morphine content is of especial importance in showing that the sample is within the usual range for opium of the region in question. When the morphine content shows the sample to be greatly substandard the charts are not applicable as they stand, but conclusions can still be drawn from the ratios of the other alkaloids to morphine and to each other.

Methods for narcotine and meconic acid in opium have been proposed by the Government Laboratory of the United Kingdom, and the Secretariat chemists are now working on thebaine and papaverine analyses, in order that still other methods will be available when needed.

Chart 11 shows the positions on a codeine-porphyroxine chart of fifteen seizure samples attributable to India, Iran, and Turkey. In most of these cases there was also other evidence of the origin, besides the laboratory examination, but as the chart shows, the chemical evidence can be quite convincing even by itself.

Conclusions

It should not be too much to say that the determination of the origin of seized opium by physical and chemical means is now a reality. Of course, this does not mean that the origin of all seizure samples can be distinguished at the present stage of the research; it does mean that the origin of some seizures can be told now, while the origin of some others may remain in doubt even after the laboratory examination. Although some conclusions might be expressed in terms of probabilities, this is not the aim of the research. Rather, the aim is to prove the origin in specific cases "beyond a reasonable doubt". This does not mean that the origin will or can be proved by laboratory methods beyond all possible doubt, but that the evidence assembled will be entirely convincing to reasonable men. With additional tests available the proportion of seizures samples for which the origin can be determined should be increased, and the demonstrations should be even more convincing. To this end the opium studies are continuing as an international research programme.

Bibliography

1. "Opium Production Throughout the World", *Bulletin on Narcotics*, vol. 1. no. 1, October 1949.
2. "Determining the Origins of Opium", *Bulletin on Narcotics*, vol. 1, no. 1, October 1949.
3. United Nations document E/CN.7/117, 14 April 1948: A, "On determining the Country of Origin of Opium"; C, "Photomicrographs of Opium Crystals"; D, "Some Minor alkaloids of Opium, Alkaloid 1, 'Porphyroxine-Meconidine'".
4. United Nations document E/CN.7/117/Add.1, 22 September 1948. "Opium Alkaloids, Codeine".
5. United Nations document E/CN.7/117/Add.2, 22 September 1948. "Examination of Opium for Distinguishing Characteristics, Some Tentative Methods".
6. United Nations document E/CN.7/195, 22 March 1950, "The Comparative Determination of 'Porphyroxine-Meconidine' (in Opium)".
7. United Nations document E/CN.7/202, 18 September 1950, "Determination of Codeine in the Lime-Water Extract (of Opium)".

8. United Nations document E/CN.7/207, 19 October 1950, "Further Data on 'Porphyroxine-Meconidine'", by C. G. Farmilo and P. M. L. Kennett (Canada).

9. United Nations document ST/SOA/SER.K/1, 25 January 1951, "The Determination of Morphine in Opium by Extraction: A New Method".

10. United Nations document ST/SOA/SER.K/2, 11 June 1951. "The Forms of Crystals in Turkish Opium", by Alaêddin Akçasu (Turkey).

11. United Nations document ST/SOA/SER.K/3, 1 August 1951, "The Determination of Morphine in Raw Opium", by Erich Knaffl-Lenz (Austria).

12. United Nations document ST/SOA/SER.K/4, 11 September 1951, "'Porphyroxine-Meconidine' in Relation to the Origin of Opium".

13. United Nations document ST/SOA/SER.K/5, 24 September 1951, "The Ratio of Narcotine to Meconic Acid in Relation to the Origin of Opium (Preliminary Report from the Government Laboratory, London, England)". By J. R. Nicholls and E. G. Kellett (United Kingdom).

14. United Nations document ST/SOA/SER.K/6, 24 September 1951, "The Determination of Narcotine and Meconic Acid in Opium. Second Method". By J. R. Nicholls and E. G. Kellett (United Kingdom).

15. United Nations document ST/SOA/SER.K/7, 24 September 1951, "The Determination of Narcotine and Meconic Acid in Opium. Third Method". By J. R. Nicholls and E. G. Kellett (United Kingdom).

16. United Nations document ST/SOA/SER.K/8 "Codeine and Codeine-Porphyroxine Charts in Relation to the Origin of Opium".

17. "The Story of 'Porphyroxine-Meconidine'". *Bulletin on Narcotics*, vol. 4, no. 1, January 1952.

Nonaqueous Titration of Narcotics and Alkaloids[1]

By Leo Levi, P. M. Oestreicher, and Charles G. Farmilo

Twenty-five years ago, Conant, Hall, and Werner showed that many substances which exhibit little or no basic properties in water behave as relatively strong bases in glacial acetic acid and may be quantitatively determined in this solvent by titration with a strong mineral acid (1, 2).[2] Unfortunately, the potentialities of this method and its distinct advantages, as compared to many volumetric procedures carried out in aqueous media, were not immediately realized. It is only within the last two years that nonaqueous titrimetry has found a considerable number of novel applications and become a valuable analytical method of wide scope (3, 4). The studies reported in this paper demonstrate that the quantitative estimation of narcotic drugs and alkaloids of widely different structures and degrees of basicity may also be achieved by means of nonaqueous titration, using acetic acid as solvent and perchloric acid as titrant.

Experimental

Reagents and solutions

Perchloric acid 0.05 N in glacial acetic acid, prepared by dissolving approximately 4.2 ml. of perchloric acid 70-72 per cent A.C.S. grade in 1 liter of glacial acetic acid containing 25 ml. of acetic anhydride to react with any water introduced into the system (perchloric acid, water of crystallization and moisture of the sample). Standardization against N.B.S. potassium acid phthalate was performed after 24 hours standing in accordance with the procedure given by Seaman and Allen (5).

Acetic anhydride, A.C.S. grade.

Acetic acid glacial, A.C.S. grade.

Mercuric acetate solution, made up by dissolving 6 gm. of mercuric acetate C.P. in 100 ml. of hot glacial acetic acid and allowing to come to room temperature.

Methyl violet (6B) indicator solution, prepared by dissolving 0.1 gm. of dye in 100 ml. of glacial acetic acid.

Analytical procedures

All compounds except the halide acid salts were analysed by dissolving about 0.5 milliequivalents in 80 ml. of glacial acetic acid and titrating directly with 0.05 N perchloric acid to a blue-green end point. A microburet calibrated to 0.01 ml. was used for measuring the volume of acid consumed.

The halide acid salts were dissolved in 80 ml. of glacial acetic acid, reacted with 5 ml. of 6 per cent mercuric acetate solution and subsequently neutralized by means of perchloric acid as indicated above. A magnetic stirrer was used to carry out the determinations more conveniently.

Theory

Acetic acid is generally considered an amphiprotic solvent for it can act as both a proton donor and acceptor. The dissociation constant of its autoprotolysis which proceeds in accordance with the equation:

$$2\,CH_3COOH \rightleftharpoons CH_3COOH_2^+ + CH_3COO^-$$

was found by Kolthoff to be equal to 2.5×10^{-13} at 25°C. (6).

When a base B is dissolved in acetic acid the ionization process:

$$B + CH_3COOH \rightleftharpoons BH^+ + CH_3COO^-$$

takes place to an appreciable extent and even with bases that are considered weak in aqueous media the equilibrium of the reaction lies far to the right. This "levelling effect" of the solvent was first observed by Hall who showed by means of electrochemical measurements that all bases stronger than aniline, which is a very weak base in water ($pK_A=4.75$), are of considerable and almost equal strength in acetic acid solution (7, 8). It is evident that in these reactions the solvent displays strong protogenic or acidic properties.

Addition of perchloric acid to acetic acid is associated with the formation of a solvated proton:

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ + ClO_4^-$$

and under normal conditions this reaction tends to go to completion (6, 9). Hence, in a perchloric acid-acetic acid mixture, acetic acid displays protophilic or

[1] Contribution from the Organic Chemistry and Narcotic Section, Food and Drug Laboratories, Department of National Health and Welfare, Ottawa, Canada.

[2] Figures in parentheses indicate items within the list of references to be found at the end of this article.

basic properties. The solvated ion generated is a powerful proton donor, i.e., an acid of exceptional strength. It will readily neutralize any base that is stronger than the solvent itself and the fundamental process underlying nonaqueous titration of bases in glacial acetic acid by means of perchloric acid may thus be visualized to proceed in the following manner:

$$B + CH_3COOH \rightleftharpoons BH^+ + CH_3COO^-$$

$$CH_3COO^- + CH_3COOH_2^+ + ClO_4^- =$$

$$2\,CH_3COOH + ClO_4^-$$

Salts of organic bases — except sulfates and halides — are neutralized in a similar fashion as may be shown for codeine phosphate:

$$C_{18}H_{21}NO_3 \cdot H_3PO_4 \rightleftharpoons C_{18}H_{21}NO_3H^+ + H_2PO_4^-$$

$$H_2PO_4^- + CH_3COOH_2^+ = H_3PO_4 + CH_3COOH$$

Sulfates are titrated to bisulfates only because the in the reaction

$$SO_4^{--} + H^+ \text{(acetic acid)} \rightleftharpoons HSO_4^-$$

the equilibrium lies far to the right whereas in the succeeding reaction

$$HSO_4^- + H^+ \text{(acetic acid)} \rightleftharpoons H_2SO_4$$

it lies far to the left. Bisulfates therefore do not behave as bases in glacial acetic acid (10).

Halide ions are extremely weak bases and the reaction

$$X^- + CH_3COOH_2^+ \rightleftharpoons HX + CH_3COOH$$

does not go to completion, the strong mineral acid generated during the titration causing the end point to occur long before the equivalence point is reached.

Correct results can be obtained however by either boiling the solution to volatilize the hydrogen halide formed and thereby force the reaction to completion — a method analogous to the titration of carbonates in aqueous solution — or by adding to the system prior to titration a slight excess of mercuric acetate so as to convert the anion to undissociated mercuric halide which will not take part in the neutralization process (11, 12). The latter procedure is to be preferred because of the tendency of many organic compounds to decompose on prolonged boiling. The reaction appears to proceed in accordance with the following scheme:

$$R_3N \cdot HX + 1/2\ Hg(CH_3COO)_2 =$$

$$R_3NH^+ + CH_3COO^- + 1/2\,HgX_2$$

$$CH_3COO + CH_3COOH_2^+ = 2\,CH_3COOH$$

Experimental Results and Discussion

The results of the analyses presented in table I illustrate that a variety of narcotics and alkaloids may be accurately determined in glacial acetic acid by titration with perchloric acid. The compounds investigated comprise diarylalkoneamines, arylpiperidines, benzylisoquinolines, and hydrophenanthrenes containing an imino-ethano linkage. These amines are only slightly soluble in water and because of their weakly basic character most of them cannot be determined in aqueous media with a high degree of precision. The structural formulae of the organic bases are shown in column 1 and their aqueous dissociation constant exponents, determined in accordance with the method of Saunders, given in column 3 (13). Papaverine, phenadoxone, pipidone, and narcotine, for example, with pK_A values less than 7, did not show any inflection in their titration curves when water was used as solvent and nonaqueous titrimetry offers a valuable direct method for their quantitative determination. In accordance with the theoretical considerations given morphine sulphate used but one mole of perchloric acid for complete neutralization:

$$(C_{17}H_{19}NO_3 \cdot H)_2 \cdot SO_4 + CH_3COOH_2^+ =$$

$$2\,C_{17}H_{19}NO_3H^+ + HSO_4^- + CH_3COOH$$

whereas morphine tartrate consumed two moles of titrant per mole — see column 5 — because the tartrate ion which is neutralized carries two negative charges:

$$(MH)_2^{++} + \begin{matrix} CHOHCOO^- \\ | \\ CHOHCOO^- \end{matrix} + 2\,ClO_4^- + 2\,CH_3COOH_2^+ =$$

$$(MH)_2^{++} + 2\,ClO_4^- + (CHOHCOOH)_2 + 2\,CH_3COOH$$

Dihydrocodeinone and dromoran (*l*-3-hydroxy-N-methyl morphinan) tartrate however consumed only one mole of perchloric acid per mole because the tartrate ion which is titrated in these instances carries but one negative charge:

$$BH^+ + \begin{matrix} CHOHCOO^- \\ | \\ CHOHCOO \end{matrix} + ClO_4^- + CH_3COOH_2^+ =$$

$$BH^+ + ClO_4^- + (CHOHCOOH)_2 + CH_3COOH$$

Pseudomorphine was found to consume two equivalents of perchloric acid per mole as expected because two acetate ions are affected by the titration. In column 6 results of analyses using official and industrial control methods are given and it is evident that good agreement exists with the results obtained by titration with perchloric acid (column 4).

The quantitative estimation of morphine-N-oxide by means of perchloric acid is of particular interest since

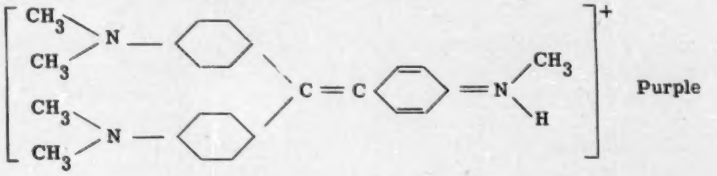
it represents — to the best of our knowledge — the first reported nonaqueous titration of an amine oxide. It is to be realized that, whereas the basicity of an amine is determined by the reactivity of the unshared pair of electrons associated with the nitrogen atom, the basic character of an amine oxide is a function of the oxygen rather than of the nitrogen atom for there is on the latter no lone electron pair to which a proton could become attached. Hence formation of the perchlorate of an amine oxide in acetic acid is comparable to the formation of its halide acid salt in water. However, most amine oxides are not sufficiently basic to be titratable with halide acids in aqueous media. With morphine-N-oxide for example no potential break whatever can be detected during titration in water with a 0.05 N aqueous hydrochloric acid solution whereas titration in glacial acetic acid with a perchloric acid solution of comparable strength is associated with a distinct colour change at the equivalence point. Since tribenzylamine oxide can also be determined by means of perchloric acid (14) it may well be that amine oxides in general fall within the scope of this method and that other heterocyclic compounds whose basicity and capability of salt formation are due to the presence of unshared pairs of electrons associated with an oxygen atom, e.g., pyrones and related compounds may also be estimated by titrimetry in nonaqueous solvents.

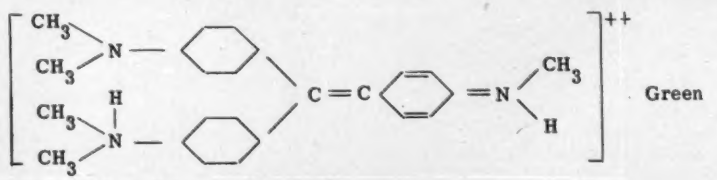
In addition to its application to pure compounds, as shown in table I, the method has been successfully used for some time in this laboratory for the rapid and accurate analysis of narcotic seizures. Non-ionizing adulterants such as starch, sucrose, lactose, aspirin, etc., do not show any interference but since anions react with perchloric acid an excipient like calcium carbonate for example would affect the titration and should be removed from the sample in order to avoid erroneous titration values. The presence or absence of nitrogen containing diluents, such as quinine, novocaine, and amidone, which are occasionally encountered in illicit samples must, of necessity, also be established and corrected for prior to analysis.

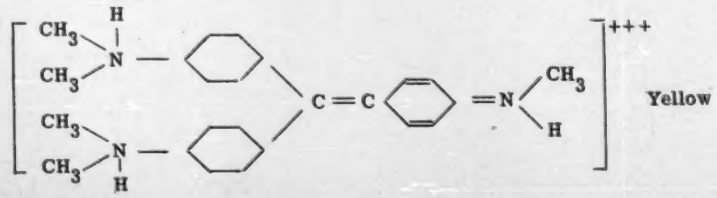
In all titrations vivid colour changes accompanied the approach of the equivalence point and two or three drops (approximately 0.03 ml.) of the titrant were always sufficient to change the colour of the solution from the last shade of blue to a faint green.

Methyl violet, the indicator used, shows a variety of colours in glacial acetic acid depending on the pH of the solution. These colours were observed by titrating 30 ml. of a solution containing 3.8×10^{-7} moles of methyl violet (pentamethyl-p-rosaniline hydrochloride) per litre with 0.009196 N perchloric acid. It was found that 0.110 ml. of the acid changed the colour of the indicator from purple to blue, 0.161 ml. from blue to green and 1.650 ml. from green to yellow.

The spectral curves shown in figure 1 illustrate the absorption of the indicator at these three levels of perchloric acid titration. They resemble those obtained by Conant and Werner on crystal violet (hexamethyl-p-rosaniline hydrochloride) in buffered glacial acetic acid systems but show that additional maxima and another isobestic point occur below 475 mμ which region these workers had left unexplored (15). Since the addition of perchloric acid to a solution of methyl violet in glacial acetic acid is associated with progressive protonation of the indicator the isobestic points occurring at about 350, 500 and 725 mμ may be visualized as corresponding to formation of the three ionic species:







Some of the compounds assayed, e.g., dihydrocodeinone, formed perchlorates which were only partially soluble in the solvent system used and precipitated during the titration. However this phenomenon did not reduce the sharpness of the indicator end point. Solutions of apomorphine in glacial acetic acid developed a blue coloration on standing and had to be titrated fairly rapidly to obtain accurate assay values. It was also found important to carry out all determinations under essentially anhydrous conditions for the sharpness of the indicator end point was noticeably impaired by the presence of about 2 per cent of water, and the volume of titrant consumed in such cases exceeded always the stoichiometrically required amount — apparently because of the weakly basic properties inherently exhibited by water:

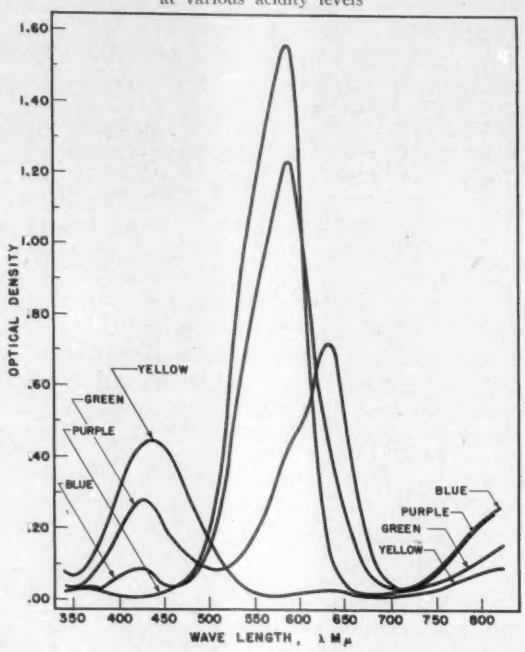
$$CH_3COOH_2^+ + H_2O \rightleftharpoons CH_3COOH + H_3O^+$$

The use of a slight excess of acetic anhydride helped prevent such interference. Another factor that had to be taken into account is the rather large coefficient of cubical expansion of glacial acetic acid which amounts to 0.11 per cent per °C (5). In order to obtain accurate results the titrant was therefore always standardized and used at the same temperature. Provided these precautions were met replicate determinations agreed very closely and a precision of ±0.3 per cent was easily realized. This value compares favourably with that obtained by conventional aqueous acidimetric and alkalimetric titrations.

Summary and Evaluation of the Method

The data presented show that nonaqueous titrimetry permits the rapid and accurate direct determination of narcotic bases and, *inter alia*, the quantitative estimation of the physiologically active moiety of the molecule if it occurs as the salt of an organic or inorganic acid. The apparatus needed to carry out these analyses is inexpensive and available in any laboratory equipped to do aqueous titrations. The method itself is free from all processes of time-consuming extractions, chromatographic separations, formation of insoluble derivatives under controlled conditions, and reference to colorimetric standards, which techniques characterize most official and industrial procedures. It should prove of particular value to toxicologists and forensic chemists concerned with the quantitative evaluation of these drugs.

Figure I
Absorption spectra of methyl violet (6B) in glacial acetic acid at various acidity levels



Acknowledgments

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References

(1) Conant, J. B. and Hall, N. F., *J. Am. Chem. Soc., 49,* 3047 (1927).
(2) Hall, N. F. and Werner, T. H., *J. Am. Chem. Soc., 50,* 2367 (1928).
(3) Riddick, J. R., *Anal. Chem., 24,* 41 (1952).
(4) Fritz, J. S., *Acid-Base Titrations in Nonaqueous Solvents,* The G. Frederick Smith Chemical Company, Columbus, Ohio (1952).
(5) Seaman, W. and Allen, E., *Anal. Chem., 23,* 592 (1951).
(6) Kolthoff, I. M. and Willman, A., *J. Am. Chem. Soc., 56,* 1007 (1934).
(7) Hantzsch, A., *Zeitschr. Physik. Chem., 134,* 406 (1928).
(8) Hall, N. F., *Chem. Reviews, 8,* 191 (1931); *J. Am. Chem. Soc., 52,* 5115 (1930).
(9) MacKenzie, H. A. E. and Winter, E. R. S., *Trans. Farad. Soc., 44,* 159 (1948).
(10) Pifer, Ch. W. and Wollish, E. G., *Anal. Chem., 24,* 519 (1952).
(11) Higuchi, I. and Concha, J., *Science, 113,* 210 (1951).
(12) Pifer, Ch. W. and Wollish, E. G., *Anal. Chem., 24,* 300 (1952).
(13) Saunders, L. and Srivastava, R. S., *Journ. Pharm. and Pharmac., 3,* 78 (1951).
(14) Davis, M. M., National Bureau of Standards, Washington, D.C., Private Communication.
(15) Conant, J. B., and Werner, T. H., *J. Am. Chem. Soc., 52,* 4436 (1930).

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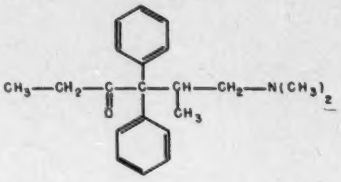
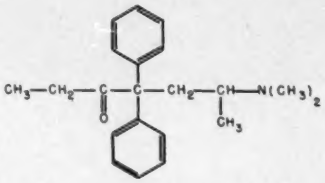
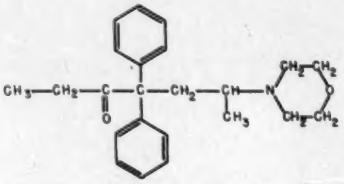
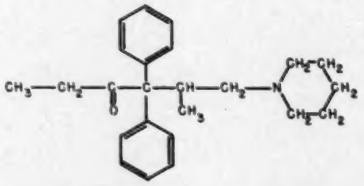
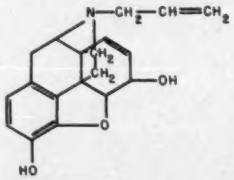
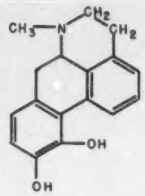
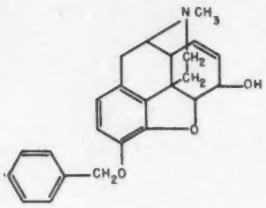
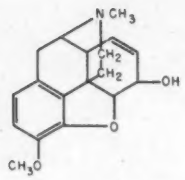
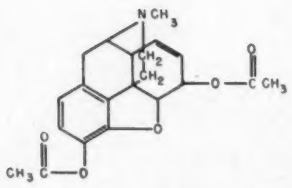
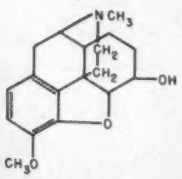
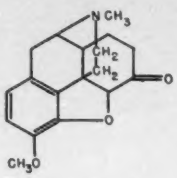
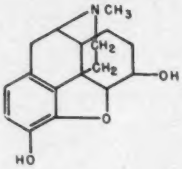
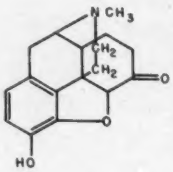
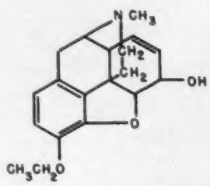
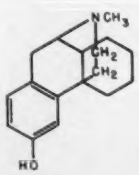
Table I. Nonaqueous titration of narcotics and alkaloids by means of perchloric acid

Structural formula of free base	*Compound*	pK_A *of base in water (20° C.)*	*Per cent recovery by:* Nonaqueous Titration	*Per cent recovery by:* Reference Assay	*Average gram equivalent HClO per mole[4] of compound*
	ALKANONEAMINES				
	Isomethadone.HCl	8.07	94.65 94.47 94.56	—	0.9456
	Methadone.HCl	8.25	99.27 99.04 99.16	99.13[1]	0.9916
	Phenadoxone.HCl	6.89	99.63 99.79 99.88	99.91[2]	0.9977
	Pipidone.HCl	6.80	98.96 98.78 99.01	—	0.9892
	HYDROPHENANTHRENES				
	N-Allylnormorphine.HCl	7.83	98.90 99.23	—	0.9907

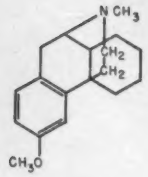
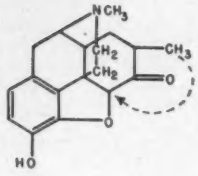
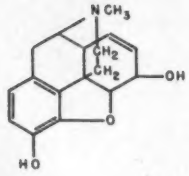
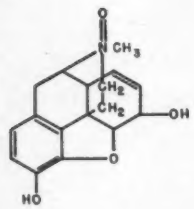
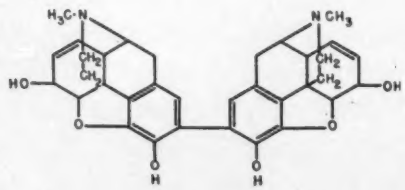
[1] N.N.R.1951.
[2] Control method of Glaxo Laboratories.

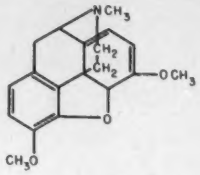
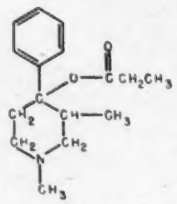
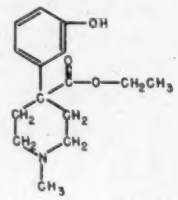
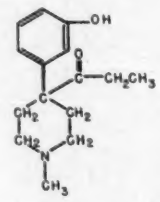
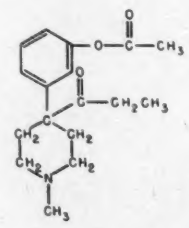
Structural formula of free base	Compound	pK_A of base in water (20° C.)	Per cent recovery by: Nonaqueous Titration	Per cent recovery by: Reference Assay	Average gram equivalent HClO per mole[1] of compound
	HYDROPHENANTHRENES (continued)				
	Apomorphine.HCl.½H_2O	7.17	98.61 98.20	—	0.9840
	Benzylmorphine.HCl	8.07	99.98 96.73 100.0	—	0.9990
	Codeine.H_3PO_4.½H_2O	8.22	95.64 96.01 95.88	96.07[3]	0.9584
	Diamorphine.HCl	7.83	100.3 100.1 100.4	100.3[4]	1.003
	Dihydrocodeine	8.68	100.1 99.85 99.79	—	0.9991

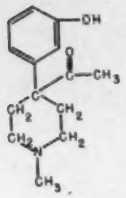
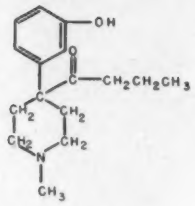
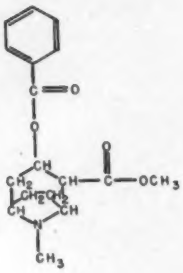
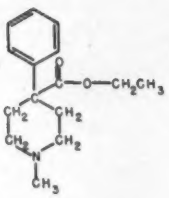
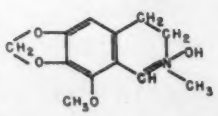
[3] B.P.1948.
[4] A.O.A.C.1950.

Structural formula of free base	*Compound*	*pKA of base in water (20° C.)*	*Per cent recovery by: Nonaqueous Titration*	*Per cent recovery by: Reference Assay*	*Average gram equivalent HClO per mole[1] of compound*
	HYDROPHENANTHRENES (continued)				
	Dihydrocodeinone. $(CHOHCOOH)_2.2\frac{1}{2}\ H_2O$	6.61	99.63 99.47 99.74	—	0.9961
	Dihydromorphine.$1H_2O$	8.55	97.33 97.60 97.54	—	0.9749
	Dihydromorphinone.HCl	8.15	97.00 96.81 97.08	96.71[5]	0.9696
	Ethylmorphine.HCl.$2H_2O$	8.20	99.97 99.76 100.0	—	0.9997
	*l*-3-Hydroxy-N-methyl-morphinan. $(CHOHCOOH)_2.2H_2O$	8.18	99.13 99.51	—	0.9932
	Methorphinan.HBr.$\frac{1}{2}H_2O$	8.97	98.79 98.84 98.90	98.93[6]	0.9884

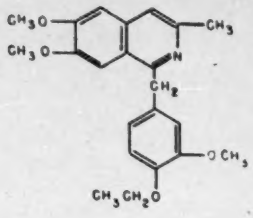
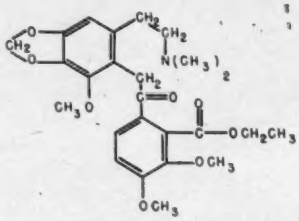
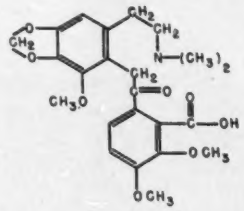
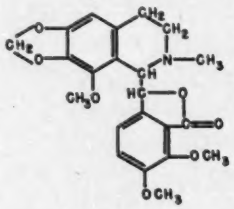
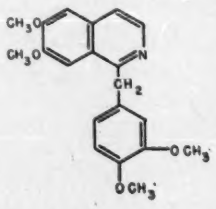
[5] U.S.P.XIV.
[6] Control method of Hoffmann-LaRoche.

Structural formula of free base	Compound	pK_A of base in water (20° C.)	Per cent recovery by: Nonaqueous Titration	Per cent recovery by: Reference Assay	Average gram equivalent HClO per mole[4] of compound
	HYDROPHENANTHRENES (continued)				
	*dl*-Methoxydromoran.HBr. $2H_2O$	8.83	98.96 98.57	—	0.9876
	Metopon.HCl	8.08	99.42 99.83 99.68	—	0.9964
	Morphine.HCl.$3H_2O$	8.05	96.01 96.34 96.28	96.18[3]	0.9621
	Morphine Meconate.$5H_2O$	—	96.41 96.18	—	1.9259
	Morphine Sulfate $(Morphine)_2.H_2SO_4.5H_2O$	8.02	95.82 96.20	96.13[3]	0.9601
	Morphine Tartrate $(Morphine)_2.(CHOHCOOH)_2.3H_2O$	8.07	98.81 98.50	—	1.9732
	Morphine-N-oxide	4.82	99.18 99.31 99.44	—	0.9931
	Pseudomorphine	—	98.08 98.34	—	1.9642

Structural formula of free base	*Compound*	*pKA of base in water (20° C.)*	*Per cent recovery by: Nonaqueous Titration*	*Reference Assay*	*Average gram equivalent HClO per mole[4] of compound*
	HYDROPHENANTHRENES (continued)				
	Thebaine	8.15	98.86 99.03 98.77	—	0.9889
	ARYLPIPERIDINES				
	Alphaprodine.HCl	8.73	99.74 99.51 99.60	99.40[6]	0.9962
	Bemidone.HCl	8.62	97.94 97.76 98.05	—	0.9792
	Ketobemidone.HCl	8.67	98.73 99.03 98.95	—	0.9890
	Acetoxyketobemidone	8.75	98.76 99.00 99.08	—	0.9895

Structural formula of free base	Compound	pKA of base in water (20° C.)	Per cent recovery by: Nonaqueous Titration	Per cent recovery by: Reference Assay	Average gram equivalent HClO per mole[1] of compound
	ARYLPIPERIDINES (continued)				
	Methylketobemidone.HCl	8.61	99.13 98.74 98.83	—	0.9890
	Propylketobemidone	8.62	99.94 100.0 99.68	—	0.9988
	Cocaine.HCl	8.60	99.02 98.73 98.86	98.41[7]	0.9887
	Pethidine.HCl	8.72	96.99 96.78 97.02	96.83[5]	0.9693
	BENZYLISOQUINOLINES				
	Cotarnine	—	99.79 100.1	—	0.9994

[7] N.F.VIII.

Structural formula of free base	Compound	pKA of base in water (20° C.)	Per cent recovery by: Nonaqueous Titration	Per cent recovery by: Reference Assay	Average gram equivalent HClO per mole[4] of compound
	BENZYLISOQUINOLINES (continued)				
	Dioxyline.H_3PO_4.½H_2O	—	98.24 97.88	—	0.9806
	Ethylnarceine.HCl	8.04	97.98 98.27	—	0.9813
	Narceine.3H_2O	3.76	97.15 96.78	—	0.9697
	Narcotine.HCl.1H_2O	6.24	100.0 99.63 99.87	—	0.9983
	Papaverine.HCl	5.98	98.74 98.58 98.62	98.50[5]	0.9865

Detection of Morphine in *Papaver setigerum* DC

By C. G. Farmilo,[1] H. L. J. Rhodes,[2] H. R. L. Hart[3] and H. Taylor[4]

1. Chemical analyses by C. G. Farmilo and H. R. L. Hart

2. Botanical classification of Papaver setigerum *by H. L. J. Rhodes*

3. Photography by H. Taylor

Introduction

Morphine was first isolated from the dried latex obtained from capsules of *Papaver somniferum* soon after 1800. It was the first alkaloid discovered. Recent reviewers (1),[5] (2), (3), (4) do not entirely agree as to the man who first discovered morphine. Although Derosne (5) described the isolation of a "salt of opium" in 1803, apparently the chief credit for the discovery of morphine should be shared by Séguin (6), whose report to the Académie des Sciences was made in 1804 but not published until 1814, and Sertürner (7) who was the first to publish a clear account, in 1805, and who gave the name "morphine" in his later work in 1817. Sertürner characterized morphine as a "vegetable alkali".

There have been some reports of finding morphine in plants other than *Papaver somniferum* but they were later found to be incorrect (8). Fulton (9) concluded in 1944 that: "At most, two or three very close relatives of *P. somniferum* (in the section Mecones of genus *Papaver*) possibly also produce morphine, but as they have not been analysed even this extension is in doubt and it is really probable only for *Papaver setigerum*" and further, "of some twenty-eight species of *Papaver* that have been examined for chromosome numbers, only *P. somniferum* and *P. setigerum* have the number 11 or a multiple [of this number] (10). Perhaps these are the only opium poppies. It seems fairly certain that *Papaver setigerum* is a true opium poppy; yet there do not seem to be any reports of actual chemical analyses" (11). Fulton's statements summarize the facts which led to the present investigation.

To definitely determine the presence of morphine in *Papaver setigerum* and to find out whether it is a "true" opium poppy, a cytogenetic, botanical, and chemical investigation has been carried out. Hart, in 1945 in co-operation with Senn and Zinck had made a preliminary survey for the presence of morphine in all poppy species that could be obtained. The results of his survey are reported here for the first time. The object of the present paper is to present botanical and cytogenetic evidence for the botanical identification of the plant *P. setigerum* and a preliminary report of the presence of morphine in *P. setigerum* which has been detected and identified for the first time. The chemical identification of morphine was carried out by means of characteristic colour and crystal reactions. The first portion of the paper presents botanical results with illustrations of the plants used and the second portion of the paper deals with chemical extraction and identification methods. Botanical descriptions of the poppies, other than *P. setigerum*, are not included.

Botanical classification of *Papaver setigerum*

Papaver setigerum DC is a poppy which grows wild in the Mediterranean region, especially in southwestern Europe. It has been cultivated as a flowering annual, but apparently is not grown in North America at the present time.

The plant is closely related to opium poppy *P. somniferum* L. and some authors have treated it as a variety or sub-species of that species. Rouy and Foucand (13) and Bonnier (12) listed it as a sub-species in floras dealing with southwestern Europe.

The cytological evidence of a close affinity between *P. setigerum* and *P. somniferum* is discussed by Fulton (14). *P. somniferum* is diploid (n=11) and *P. setigerum* is tetraploid (n=22) with exactly twice

[1] Chemist in Charge, Organic Chemistry and Narcotic Section, Food and Drug Laboratories, Department of National Health and Welfare, Ottawa, Canada.
[2] Assistant Botanist, Division of Botany and Plant Pathology, Department of Agriculture, Ottawa, Canada.
[3] Supervisory Inspector, Inspection Services (formerly Narcotic Analyst), Food and Drug Laboratories, Ottawa, Canada.
[4] Photographer, National Film Board, Ottawa, Canada.

[5] Figures in parentheses indicate items within the list of references to be found at the end of this article.

the number of chromosomes. No other species of *Papaver* is known to have the number $n=11$ or a multiple of this number. This information indicates that *P. setigerum* is not the wild ancestral species of the cultivated *P. somniferum*, as was formerly believed since a diploid would not be derived from a tetraploid plant.

The seed for the strain tested was received by Dr. C. Heimburger from the Rouen Botanical Garden, France, in 1933. Dr. Heimburger sent seed of the strain under the name *Papaver setigerum* to the Division of Botany and Plant Pathology, Ottawa, in 1945. Seed from the plants grown in 1945 was sown in 1951 to produce the plants used in the chemical analysis.

Dr. Heimburger determined the chromosome number to be $2n=44$. In 1951, Dr. R. Moore of the Division of Botany and Plant Pathology made a count of $n=22$ on flower bud material from the culture, thus confirming the earlier count. Figure 1 is a photograph of the meiotic division on which the 1951 count was based.

Originally there were both plants with violet flowers and plants with mauve flowers in the strain, but Dr. Heimburger had attempted to purify the strain by eliminating the plants with mauve flowers. He found that the violet form differed from the mauve form by one gene, with the heterozygotes intermediate.

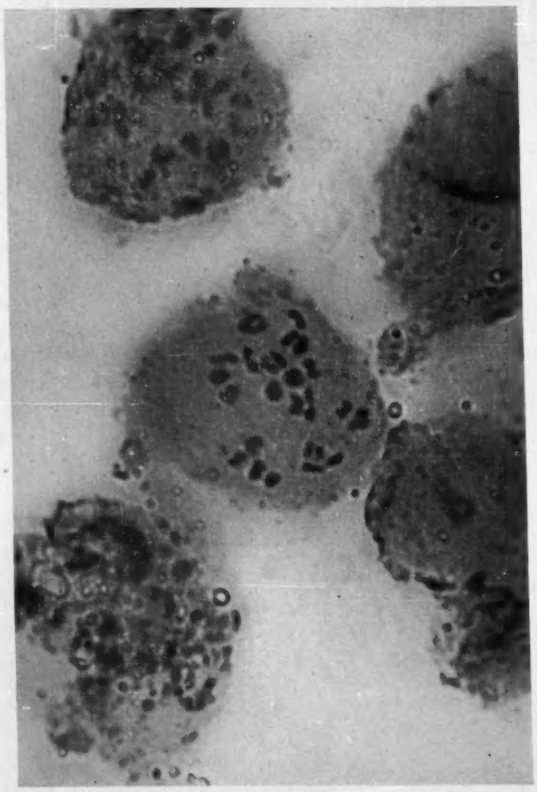


Figure 1. Meiotic division in pollen mother cell of *Papaver setigerum* DC.

The plants show the characters described for *P. setigerum* by A. P. de Candolle (15) in the original description. In general they are less coarse than plants of *P. somniferum* as usually cultivated, the flowers being smaller and the leaves thinner in texture and not glaucous (see figures 2 and 3). The teeth of the leaves are long and jagged, and each tooth is tipped with a characteristic bristle not found in *P. somniferum* (see figure 2). The buds and young peduncles are beset with setose hairs. These hairs are found more sparingly on the mature peduncles (figure 3) and along the lower midrib of the leaves. The plants closely resemble the illustration of *P. setigerum* in Bonnier (12) (figure 4) except that the hairs on the peduncles are more sparse than in Bonnier's figure.

The plants of the strain used for chemical analysis are thus identified as *Papaver setigerum* DC.

Chemical method of analysis

The following procedure was used for the extraction of morphine from *Papaver setigerum*, and only slightly modified (14) for other poppies: 50-100 grammes of dried, broken-up plant material were placed in a Waring blender with 100 ml of 95 per cent ethanol. After 10 minutes of blending the solution reached a temperature of 50°C. The blending was continued for 20 minutes and the extraction repeated twice with 100 per cent ethanol. The combined extracts were filtered using Whatman No. 40 filter paper, and the filtrate was refiltered through sintered glass. The solution of alcohol was then concentrated in an evaporating dish. The residue was treated with ether and filtered to remove the chlorophyll and plant resins. The ether-insoluble residue was treated with water (5-15 ml.) slightly acidified with acetic acid and filtered into a separatory funnel. The solution was then made alkaline to litmus with ammonia and extracted with chloroform-isopropyl alcohol (2 + 1) solution (8, 5, 2 ml. portions) and filtered into another separatory funnel. The water layer was then extracted twice with chloroform-isopropyl alcohol (3 + 1) using 10 and 5 ml. consecutive portions. The aqueous solution was then discarded. The combined chloroform-isopropanol solution was extracted with three portions (7, 5, 3 ml.) of 2 per cent aqueous sodium hydroxide solution. The first two portions of alkali solution were combined and placed in a separatory funnel, marked A. The second funnel marked B contains a 3 ml. portion of alkaline extract. The chloroform-isopropanol solution was set aside for examination of other alkaloid present. The solution in separatory funnel A was shaken twice with chloroform. Each 3 ml. portion of solvent was washed by shaking with the alkaline wash solution in separatory funnel B.

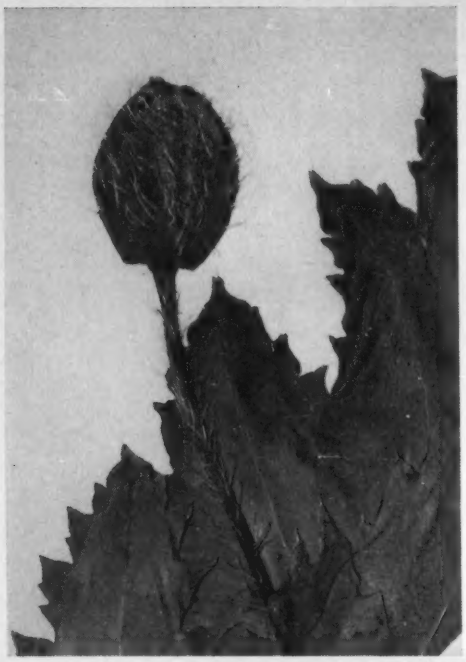


Figure 2. Photograph of *Papaver setigerum* DC plant similar to those collected for chemical analysis and determination of morphine (1950)

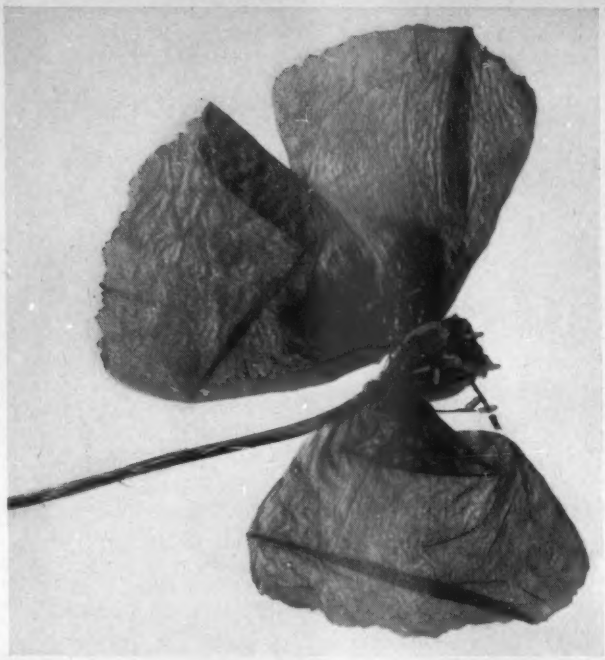


Figure 3. Photograph of dried poppy herbarium sample of *Papaver setigerum* DC collected by M. Zinck (1945)

The chloroform was then discarded. The alkaline solutions were made acid using a litmus paper indicator.

The acid solutions were extracted with chloroform to help purify the morphine extract. The solution in B was made ammoniacal, added to the separatory A, and the whole solution made ammoniacal. It was then extracted once with (2 + 1) and twice with (3 + 1) chloroform-isopropanol. The extracts were washed in funnel B with slightly ammoniacal water and then filtered into an evaporating dish. The aqueous layer was discarded and the solvent was evaporated to near dryness on a steam bath. When amounts greater than 10 mg. were obtained, recrystallization from methanol amyl-alcohol, or anisole was found successful. Ammonium chloride was added to crystallize small amounts (less than 10 mg.) of morphine from an alcohol-ether-water system.

The recrystallized residue was identified in the following manner. About 0.1 mg. of the residue was placed on a microscope slide and a drop of iodine reagent was added. The reagent was prepared from a stock solution of iodine in potassium iodide containing 10 gm. iodine and 50 gm. potassium iodide in 100 ml. water, by mixing 1 ml. of the I_2-KI solution with 3 ml. of concentrated hydrochloric and 3 ml. syrupy phosphoric acid.

The characteristic rosettes of fine needles later changing into, or growing from the solution at the same time were fine plate like structures and some individual needle crystals. These crystals were also obtained from a sample of known morphine. Another portion of the residue was tested with Marme's reagent. The fine needles characteristic of the morphine Marme complex, morphine-CdI_2 were observed. Colour tests using Fröhdes', Marquis', and Meckes' reagents, as well as ferric chloride gave the colours characteristic of morphine. It was concluded that morphine was present in the residue extracted from *Papaver setigerum.*

Results and discussion

Table I shows the results obtained by Hart in 1945 in the analysis of twenty-six species of poppies. The conclusion made on the basis of crystal and colour reactions on the residue obtained exactly according to Fulton's procedure (14) are shown in the column entitled "morphine". It is seen that only two of the species tested contained morphine; these are *Papaver somniferum* and *Papaver setigerum.* The presence of morphine in *Papaver setigerum* was confirmed by Farmilo in 1951.

Although the seeds of the opium poppy do not come under narcotic control laws generally, the question of

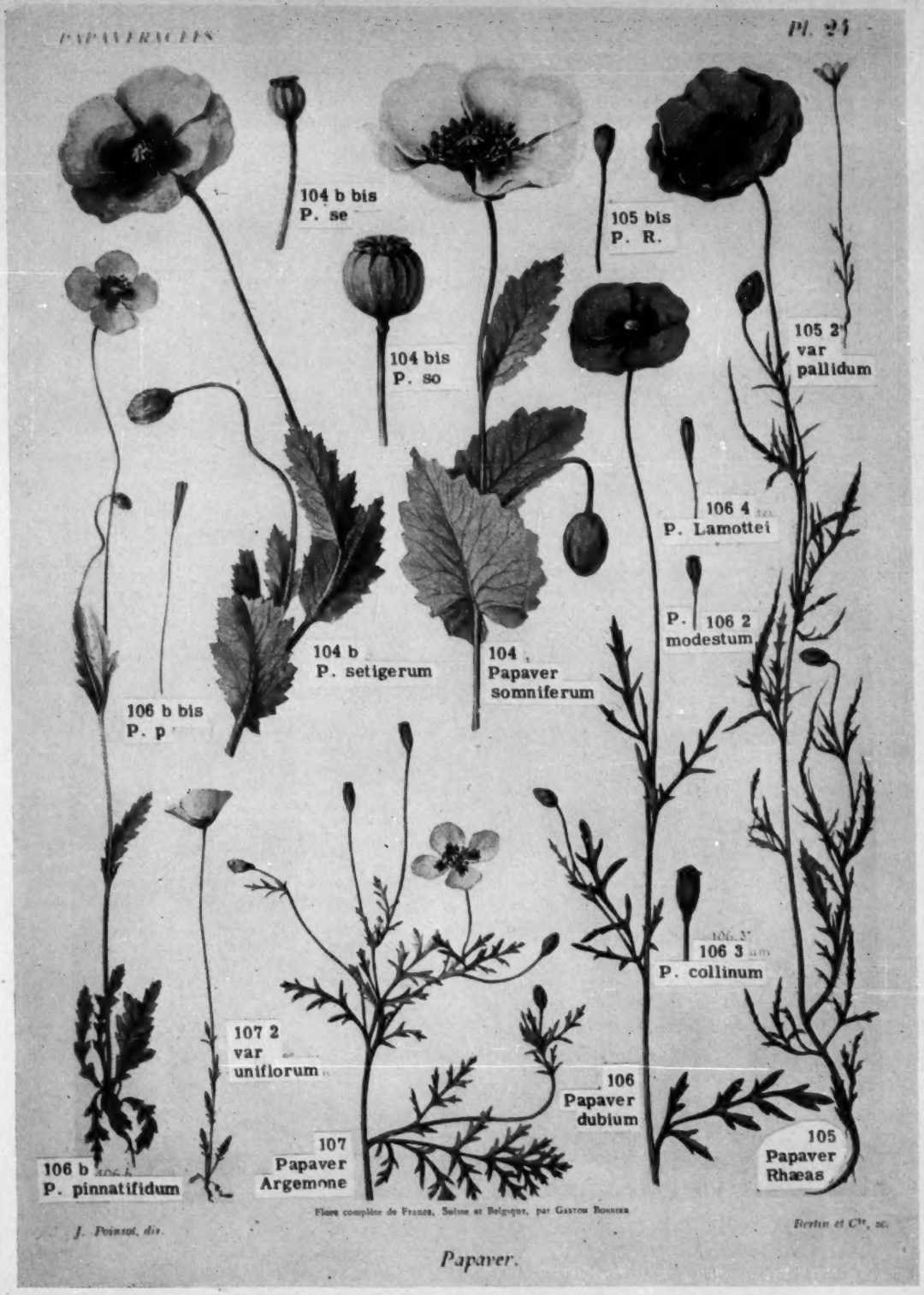


Figure 4. Illustration of some poppy plants from Gaston Bonnier (1911) showing comparison of *P. setigerum* and *P. somniferum* and others

whether certain poppy seeds are those of the opium poppy has, nevertheless, been raised on several occasions. Previously it seemed that the only way to tell was to plant the seeds and see whether morphine could by found in the resulting plant. Although the poppy seeds do not contain identifiable amounts of opium alkaloids, it now seems on the basis of cytogenetic findings that determination of the chromosome number will tell whether or not the seeds belong to an opium poppy. As far as is known, if the haploid number is 11 or a multiple of 11, the seeds belong to an opium poppy, while if the haploid number is 7 or a multiple of 7 the seeds belong to some other poppy. The chromosome numbers may be determined if some actively growing tissue (cells in the state of subdivision) such as root tip on the sprouting seed, or leaf bud on the seedling can be obtained. This is easily done within a week if the seeds sprout promptly, but sometimes it is difficult to get them to sprout in the laboratory. This process is a routine matter for the chromosome expert, but may not have occurred to the narcotic expert or chemist as a method of identification of the poppy plant, or seed. It will, therefore, be useful to narcotic agents.

Conclusions

1. *Papaverum setigerum* has been grown and identified botanically.

2. A chromosome count revealed the haploid number to be n=22. for *Papaver setigerum.*

3. Morphine has been detected in the pod, bud, and leafy parts of *Papaver setigerum* DC for the first time.

4. Twenty-four other species of poppies were examined and no morphine was found in any of them.

5. A chromosome count may be used as a means of identifying an opium poppy.

Table I. Results of survey of poppies for presence of morphine

Poppy botanical name	*No. of samples*	*Stage of growth*	*Chemical observations*					
			Marquis	*HNO_3*	*$FeCl_3$*	*Marmes*	*Bouchardats*	*Morphine*
Argemone alba	1	Bud	Brown	Brown	Green	Amorphous	Amorphous	None
	1	Pod	Brown	Brown	Green	Amorphous	Amorphous	None
Argemone barclayana	1	Bud	Brown	Brown	None	Amorphous	Amorphous	None
Argemone grandiflora	2	Bud	Brown	Red brown	None	Amorphous	Amorphous	None
	2	Pod	Brown	Brown	Green	Amorphous	Amorphous	None
Argemone mexicana	2	Bud	Brown	Red brown	Green	Amorphous	Amorphous	None
	2	Pod	Brown	Red brown	Green	Amorphous	Amorphous	None
Argemone ochroleuca	1	Pod	Brown	Brown	Green	Amorphous	Amorphous	None
Argemone platyceras rosea	1	Bud	None	(No residue obtained)				
	1	Pod	Purple	Brown	Green	Amorphous	Amorphous	None
Chelidonium majus	1	Bud	Brown	Brown	None	None	None	None
	2	Pod	Brown	Brown	None	Amorphous	None	None
Dicranostigma franchetiana	1	Bud	Red brown	Red brown	None	Amorphous	Amorphous	None
Eschscholzia californica	5	Bud	Crimson	Brown	Olive green	Amorphous	Amorphous	None
	5	Pod	Red	Brown	Green	Amorphous	Amorphous	None
Eschscholzia pulchella	2	Bud	Purple	Brown	None	Amorphous	Amorphous	None
	2	Pod	Red	Brown	Greenish	Amorphous	Amorphous	None
Glaucium sp.	1	Pod	Purple	Orange to brown	Green	Amorphous	Amorphous	None
Papaver argemone	1	Bud	Brown red	Red brown	Green	Amorphous	Amorphous	None
	2	Pod	Purple	Brown	Green	Amorphous	Amorphous	None
Papaver commitatum	2	Bud	Brown	No colour	On evaporation, green	Amorphous	Amorphous	None
	2	Pod	Brown			Amorphous	Amorphous	None
Papaver dubium	4	Bud	Brown	Red brown	None	Amorphous	Amorphous	None
	3	Pod	Brown	Brown	Finally green	Amorphous	Amorphous	None
Papaver glaucum	2	Bud	Brown	Yellow	Orange	Amorphous	Amorphous	None
	2	Pod	Brown	Brown	None	Amorphous	Amorphous	None
Papaver lateritium	1	Bud	Brown	Brown red Brown orange	Blue green	Amorphous	Amorphous	None
	1	Pod	Brown	Brown orange	None	Amorphous	Amorphous	None

Poppy botanical name	No. of samples	Stage of growth	Chemical observations					
			Marquis	HNO_3	$FeCl_3$	Marmes	Bouchardats	Morphine
Papaver monathum	1	Pod	Red to brown	Red brown	On standing, green	Amorphous	Amorphous	None
	1	Bud	Brown	Yellow	On standing, green	Amorphous	Amorphous	None
Papaver nudicaule	5	Bud	Crimson	Brown	No colour to green streaks	Amorphous	Amorphous	None
Papaver orientale	4	Pod	Red brown	Red, yellow, orange	Green	Amorphous	Amorphous	None
Papaver rhoeas	5	Bud	Red brown	Brown	None immediately, finally green	No ppt.	Amorphous	None
	5	Pod	Red brown	Brown	None immediately, finally green	Amorphous	Amorphous	None
Papaver schinzianum	1	Bud	Red brown	Brown	Green	Amorphous	Amorphous	None
	1	Pod	Red brown	Brown	Finally green	Amorphous	Amorphous	None
Papaver setigerum	2	Bud	Purple	Red	Blue green	Needles	Feathered plates	Present
	2	Pod	Purple	Red, orange, yellow, crimson orange	Blue	Needles	Feathered plates	Present
Papaver somniferum	11	Bud	Red purple	Yellow	Blue green	Needles	Crystalline	Present
	9	Pod	Red purple	Yellow red, orange yellow	Blue green	Needles	Crystalline	Present
Papaver umbrosum	1	Bud	Brown	Brown	Green	Amorphous	Amorphous	None
	1	Pod	Brown	Brown	None	Amorphous	Amorphous	None
Roemaria refracta	1	Bud	Brown	Orange	Green	Amorphous	Amorphous	None
	1	Pod	Brown	Brown yellow	Green	Amorphous	Amorphous	None

Acknowledgements

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The help of Mr. Charles Fulton from United Nations Secretariat, Narcotics Division, in giving freely expert advice and helpful discussion during the course of experiments is gratefully acknowledged, and his suggestion that a chromosome count would probably be useful for identification of an opium poppy is acknowledged.

References

(1) Holmes, H. L., *The Alkaloids, Chemistry and Physiology*, Academic Press Inc., Publishers, New York, 1952, p. 2.

(2) Henry, T. A., *The Plant Alkaloids*, Churchill, J. A., Ltd., 104 Gloucester Place, London, 1949, p. 213.

(3) Small, L. F. and Lutz, R. E., "Chemistry of the Opium Alkaloids", U. S. Govt. Printing Office, Washington, 1932, *Supplement No. 103 to the Public Health Reports, Part II*, p. 138.

(4) Weill, P. B., "The Structure of Morphine", *United Nations Bulletin on Narcotics*, vol. II, no. 2, April 1950, p. 8.

(5) Derosne, *Ann. Chim., 45*, 257 (1803).

(6) Seguin, M. A., *Ann. Chim.*, Académie des Sciences, France 1804, *92*, 225 (1814).

(7) Setürner, F. W., *Trommsdorffs Journal der Pharmazie, 13* (I) 234 (1805) 14, (I), 47 (1806); *20*, (I) 99 (1811), *Ann. Chim. et phys.*, (=) *5*, 275 (1817); *(Gilbert's) Ann. Physik, 55*, 56 (1817); *57*, 192 (1817); *59*, 50 (1818).

(8) Fulton, C. C., *The Opium Poppy and other Poppies*, U.S. Treasury Department, Bureau of Narcotics, U.S. Government Printing Office, Washington, U.S.A., 1944.

(9) Fulton, C. C., *Ibid.*, page 55, second paragraph beginning, "At most... (ending) ... setigerum".

(10) Tischler, George, *Pflanzlicher Chromosomenzahlen Tabulae Biologicae, 4*, 24, (1927); *12*, 65 (1936); *16*, 172-173 (1938).

(11) Fulton, C. C., *Same as ref. 8*, p. 38, 4th paragraph beginning "Of some... (ending) ... analyses".

(12) Bonnier, G., *Flore complète illustrée en couleurs de France, Suisse et Belgique*, Neuchâtel, Paris, Bruxelles, nouvelle édition, revue et corrigée, 1922, fasc. 4, p. 47, t. 24 fig. 104 b.

(13) Rouy, G., and Foucand, *Flore de France*, Asnières, 1893, 1:1952-153.

(14) Fulton, Charles C., *The Opium Poppy and other Poppies*, U.S. Treasury Department, Bureau of Narcotics, U.S. Government Printing Office, Washington, U.S.A., 1944, pp. 37-38.

(15) Candolle, A. P., de, *Flore Française*, Paris, 1815, 5 (suppl.): 585.

Methadone chemistry: A review

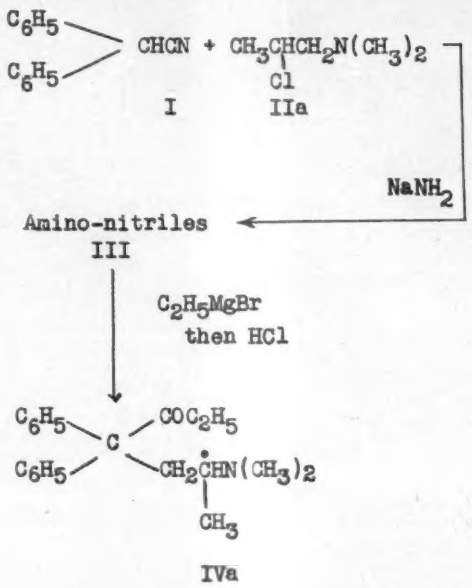
By Manuel M. Baizer, Ph.D. of the New York Quinine and Chemical Works, Inc.

In 1945 the United States Department of Commerce published (1)[1] the details of the process developed at the I.G. Farbenindustrie, Höchst am Main, for preparing the new potent morphine-like analgesic Methadone.[2] Since that time a considerable body of chemical literature has appeared dealing with the elucidation of the original process. The development of modified processes, the separation of position and optical isomers of Methadone, the formation of derivatives and transformation products and the synthesis of numerous analogues.

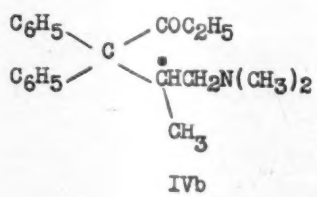
It is the purpose of this paper to review the literature that has appeared up to the end of 1951 on methadone chemistry. Brief reviews of this subject appeared in 1948 (3, 4).

Original German process

Diphenylacetonitrile (I)[3] was condensed in the presence of sodium amide with IIA, the chloroamine (B.P. 60-63° at 110 mm.; stated to be 1-dimethyl-amino-2-chloropropane) obtained by the action of thionyl chloride on 1-dimethyl-amino-2-propanol. The amino-nitrile product (III), obtained as a partially crystalline material, was brought into reaction with slightly more than two moles of ethylmagnesium bromide. The Grignard reaction product was decomposed while hot with hydrochloric acid whereupon crude Methadone[4] hydrobromide (IVA. HBr) precipitated (yield, 49.7 per cent of theory based upon III). The hydrobromide was converted to free base IVA and then to methadone hydrochloride.



Kleiderer (5) pointed out that there was an apparent discrepancy between the structure of Methadone as represented in IVa and the one which might have been expected to result from the sequence of reactions described above, namely,



That the structure of Methadone was, however, truly represented by IVa was proved in several ways:

1. Schultz, Robb and Sprague (6) showed that III obtained in the German process consisted of about equal parts of 2-dimethylamino-4,4-diphenyl-valeronitrile (IIIa) and 1-dimethylamino-2-methyl-3,3-diphenyl-butyronitrile (IIIb) and that IIIa led to Metha-

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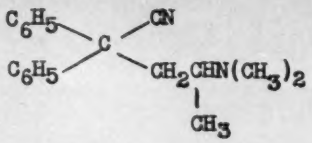
[1] Arabic figures in parentheses indicate items within the list of references to be found at the end of this article.

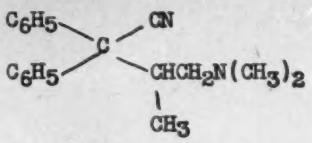
[2] This generic name, accepted by the Council on Pharmacy and Medicine of the American Medical Association (2) will be used throughout this review to denote 4,4-diphenyl-6-dimethyl-amino-3-heptanone. This substance is also known by the following names, some of which are proprietary trade-marks: Adanon, Amidone, Amidosan, AN-148, Butalgin, Depridol, Diaminon, Dianone, Dolafin, Dolamid, Dolophine, Dorexol, Heptadon, Heptanal, Hoechst 10820, Ketalgin, Mecodin, Mephenon, Miadone, Moheptan, Physeptone, Physopeptone, Polamidon, Symoran, Turanone.

[3] Roman numerals indicate reference to structures illustrated within this article.

[4] Since the molecule contains one asymetric carbon atom it is obtained in this synthesis in its dl-form.

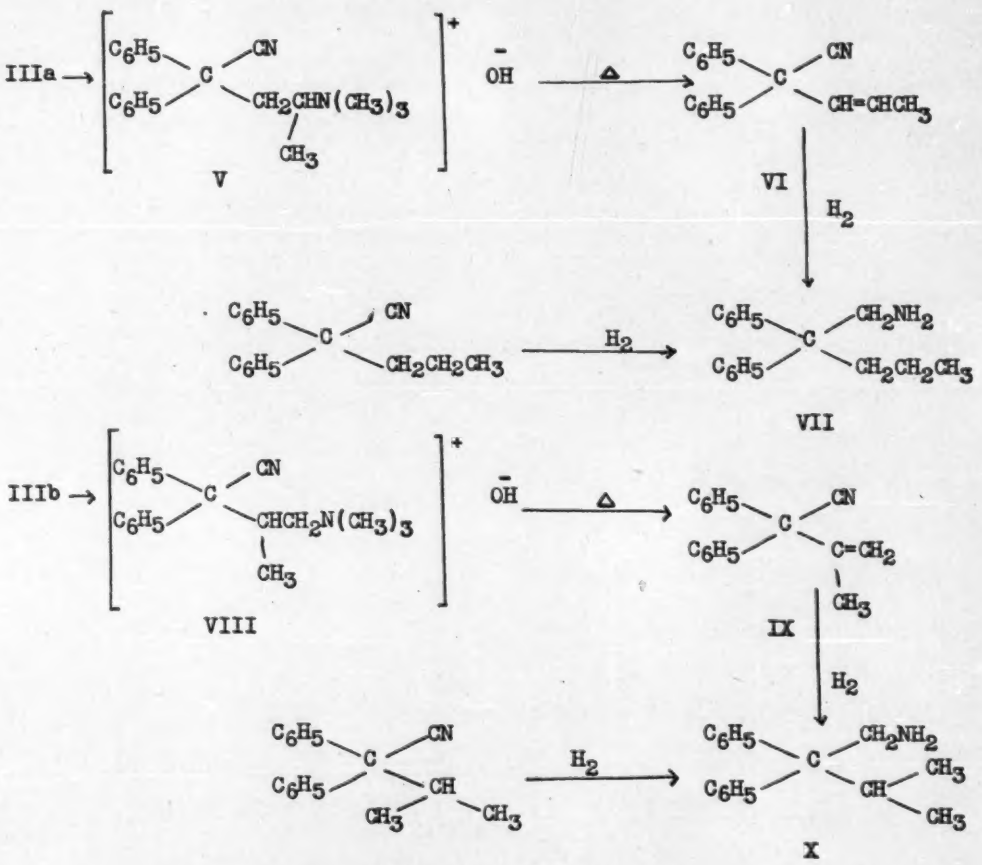


IIIa

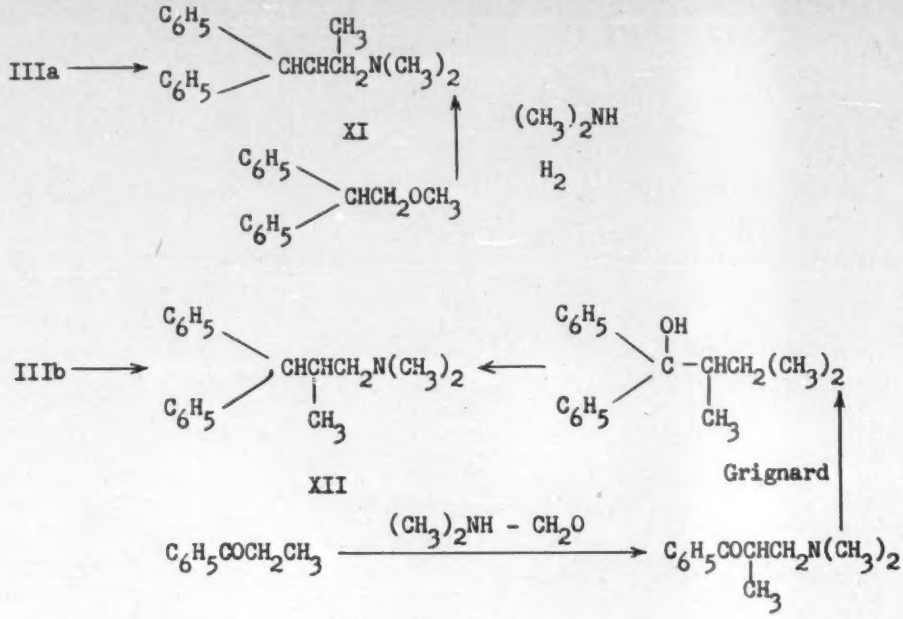


IIIb

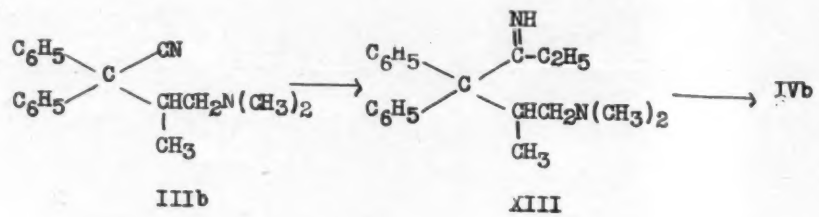
done. They proved the structure of each of the 2 amino-nitriles by the following sequence of reactions:



2. Bockmühl (7, 36) degraded IIIa and IIIb to 2-dimethylamino-4,4-diphenylbutane (XI) and 1-dimethylamino-2-methyl-3,3-diphenylpropane (XII) respectively and synthesized the latter two compounds by independant means.

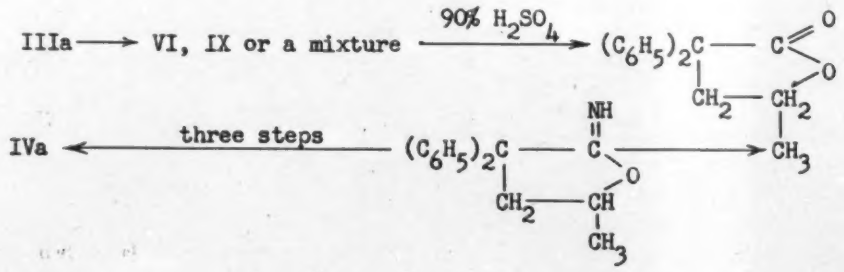


3. Easton, Gardner and Stevens' work (8) confirmed the above results and in addition demonstrated[5] that the reaction of ethylmagnesium bromide with IIIb led to the unusually stable ketimine (XIII), which on *prolonged* hydrolysis yielded isomethadone (IVb):



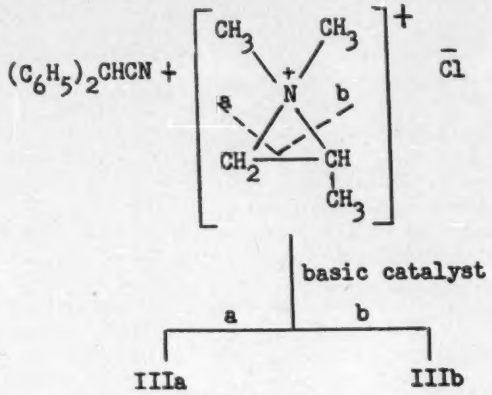
XIII and to a smaller extent IVb were present in the Mother liquors obtained after removal of Methadone hydrobromide in the original German process.

The above authors verified the structure of Methadone in a novel manner:



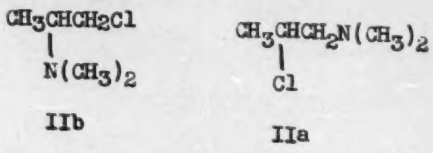
[5] Apparently anticipated by Sletzinger and Tishler (9).

The mechanism of the formation of two[6] isomeric nitriles (IIIa and IIIb) in the condensation of diphenylacetonitrile has been the subject of several inquiries. There was general acceptance of the proposal (6, 7) that a cyclic ammonium ion was probably involved which could cleave in either of two ways and thereby give rise to two products:



The point of disagreement was the interpretation of whether the cyclic ion was formed and cleaved *before* the condensation reaction or *in the course of* the condensation reaction. If the former view were correct, 1-dimethylamino-2-chloropropane (IIa) and 1-chloro-2-dimethylaminopropane (IIb) would be interconvertible and the chloroamine used in the German process would actually be an equilibrium mixture of these two isomers.[7]

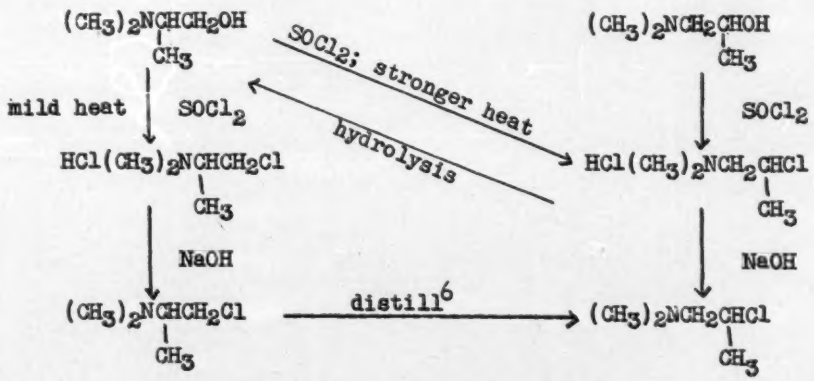
Schultz and Sprague (11) reported that 1-dimethylamino-2-chloropropane (IIa) was thermally stable but that 2-dimethylamino-1-chloropropane (IIb) rearranges to IIa on heating and that IIb hydrochloride rearranges to IIa hydrochloride. Undistilled IIb liberated at a low temperature from its hydrochloride and condensed with diphenylacetonitrile yielded a mixture of the isomeric nitriles IIIa and IIIb. These authors concluded therefore that arrangement occurs in the course of the condensation of the chloroamine with the diphenylacetonitrile anion (basic catalyst present).



Walton, Ofner and Thorp (12) confirmed the above work, but Brode and Hill (13) held that both IIa and IIb rearranged, under the conditions used to liberate them from their respective hydrochlorides, to an equilibrium mixture of the two. Attenburrow, *et al.*, (14) found that IIb was not thermally unstable and did not isomerize during distillation.[8]

The entire question of the isomerism of the chloroamines was later re-examined by Ofner (10) whose results are summarized in the chart below:[9]

Ofner concluded that the mixture of amino-nitriles (IIIa and IIIb) obtained in the reaction between diphenylacetonitrile and either 1-dimethylamino-2-chloropropane or 1-chloro-2-dimethylaminopropane must be due to the rearrangement of the chloroamine in the presence of the diphenylacetonitrile anion. The ratio of the amino-nitrile isomers obtained varies with the nature of the basic group of the chloro-amine employed in the alkylation.



[6] A third structural isomer of Methadone presumably arising from a third isomeric nitrile has been reported (8b) but not verified by other investigators.

[7] The ratio of the two isomers might then vary according to the conditions used in the liberation of the chloroamine from its hydrohalide salt. *Cf.* (10).

[8] The following chart has been taken from the article referred to and is reproduced by permission of the publishers of the *Journal of the Chemical Society*.

[9] This thermal rearrangement contradicts the work of Attenburrow, *et al.* (14).

Summary

1. The condensation between diphenylacetonitrile and 1-dimethylamino-2-chloropropane according to the German process gives rise to two isomeric nitriles IIIa and IIIb in approximately equal amounts.

2. The Grignard reaction between ethylmagnesium bromide and the mixture of isomeric nitriles, followed by the ordinary acid hydrolysis, yields methadone hydrobromide as a precipitate and leaves the ketimine of isomethadone (XIII, as hydrohalide salt) in the aqueous Mother liquor. This ketimine can be converted to isomethadone by prolonged boiling with concentrated hydrochloric or hydrobromic acid.

Variations on the German process

1. *Diphenylacetonitrile:* The mode of preparation of this intermediate is not specified in P B Report 981 (1). However, need for it in the preparation of Methadone and certain analogues has stimulated the development of several very satisfactory syntheses (15).

2. *Condensing agent:* In place of sodium amide, lithium amide (16), potassium tert-butoxide (6) and sodium hydroxide (17) have been used.

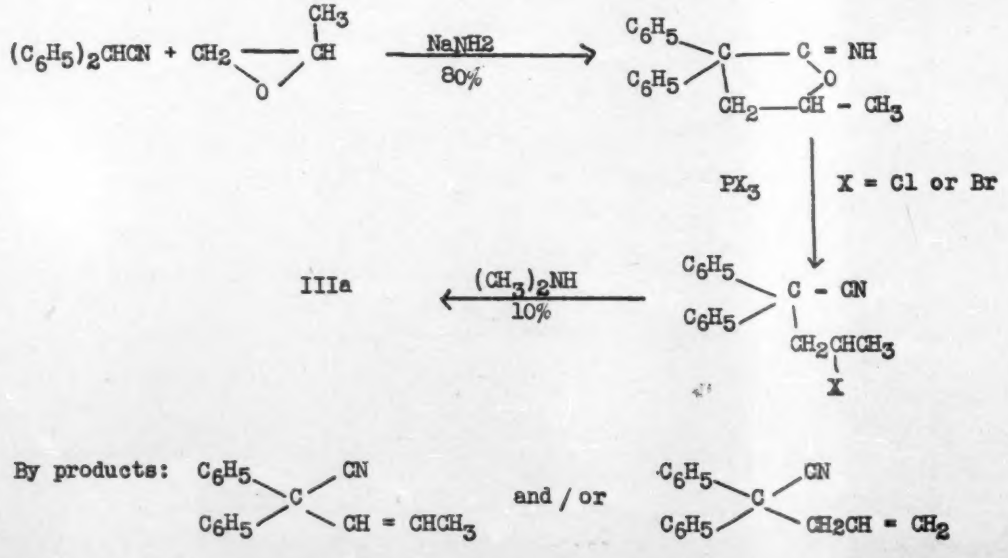
3. *Separation of the isomeric nitriles IIIa and IIIb:* This separation was not effected in the original process. The higher melting isomer IIIa, is less soluble than IIIb in hexane (6) or "aliphatic alcohols, saturated aliphatic hydrocarbons and aliphatic ketones" (18). On the other hand IIIb forms the more insoluble salts with P-toluenesulphonic acid (19) or oxalic acid (18).

IIIa, on treatment with ethylmagnesium bromide, followed by hydrolysis of the Grignard complex, yield methadone in 89 per cent yield (20). An improvement, involving essentially the addition of the Grignard complex to acid rather than the usual reverse procedure, is claimed to lead to improved yields (ca. 90 per cent) (21).

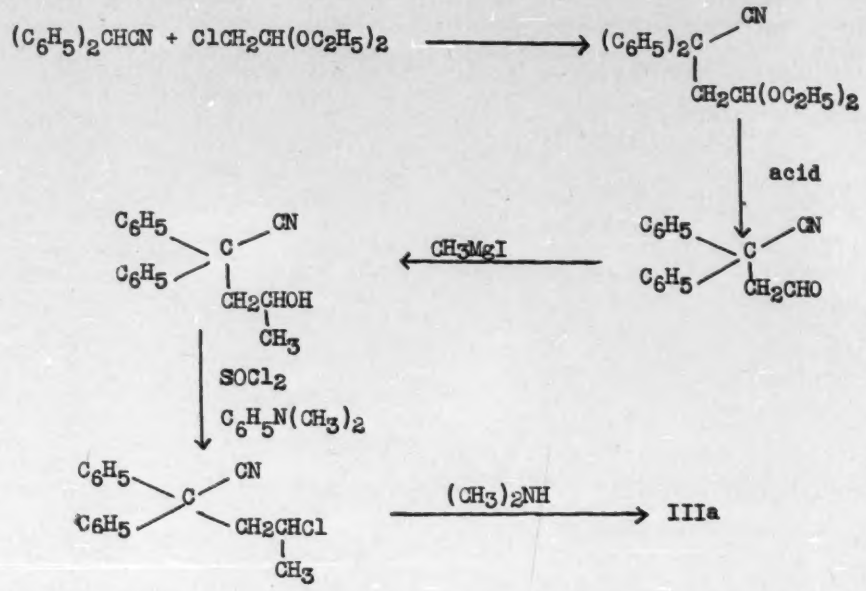
Other Methadone processes

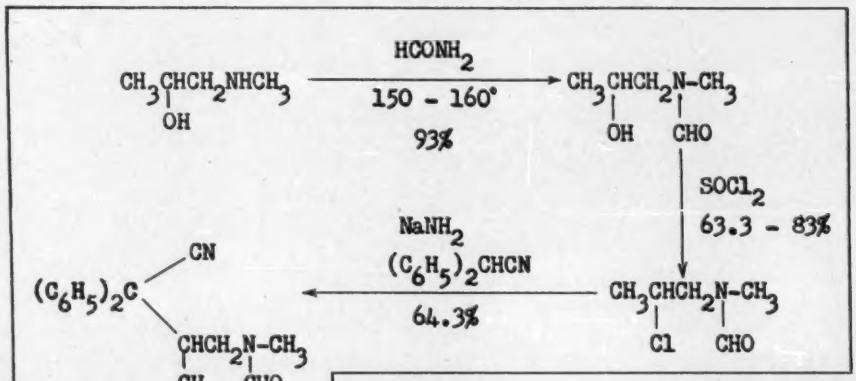
As pharmacological data on the methadones were accumulated, it appeared first that DL-methadone and later that D1-isomethadone would be the more therapeutically important structural isomer (the question of optical isomers is considered below). Efforts were therefore directed toward devising syntheses which would yield one or the other isomer alone, and not, as in the German process, a mixture of nitriles leading to two products. To achieve this it was obviously necessary to avoid the use of a halo-tert-amine and to condense diphenylacetonitrile with a potential three-carbon moiety containing a functional group convertible to a properly situated dimethylamino-group.

Easton, *et al.* (22), devised the following sequence leading to IIIa, the nitrile precursor of Methadone. Yields in the last step were poor, an important side reaction being the dehydrohalogenation produced by dimethylamine.

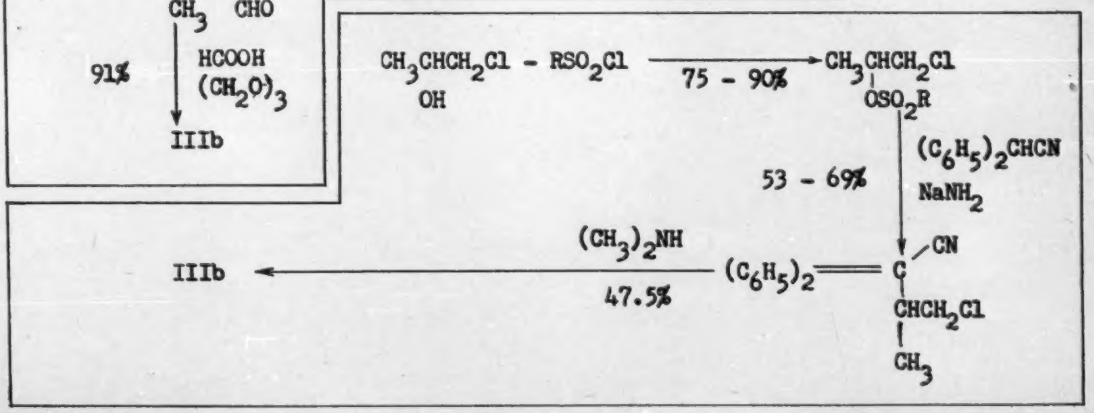


Morrison and Rinderknecht (23) employed the diethylacetal of chloroacetaldehyde as the source of the "side-chain":



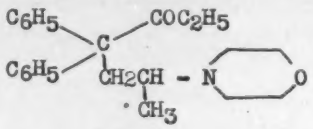


Two United States patents have been issued recently (24, 25) on ingenious processes leading exclusively to IIIb, the amino-nitrile precursor of isomethadone, IVb. The steps involved in each are given schematically below:



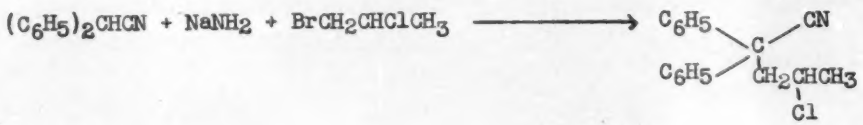
Attempts to obtain a methadone directly by condensing 4, 4-diphenyl-3-butanone with 1-dimethyamino-2-chloropropane were not successful (12).

Other types of processes have been studied in connexion with the preparation of methadone analogues, particularly the morpholino-analogues XIV.



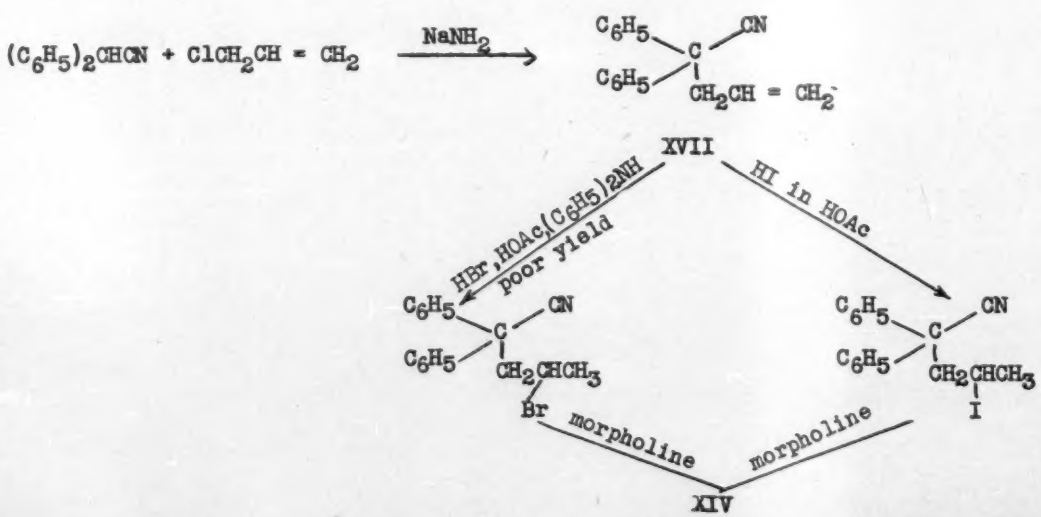
XIV

In one process (26) the sodio-derivative of diphenylacetonitrile was condensed with 1-bromo-2-chloropropane. The greater reactivity of bromine relative to chlorine permitted the preparation of 2-chloro-4,4-diphenylvaleronitrate, XV, in 47.5 per cent yield:



XV

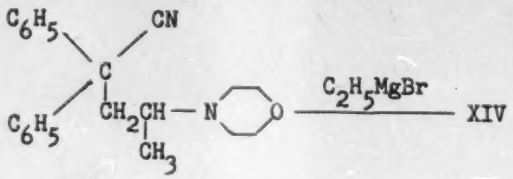
In another process (27) diphenylacetonitrile was condensed with allyl chloride. Addition of hydrogen bromide or hydrogen iodide to the resultant olefin (XVII) yielded a 2-halo-4,4-diphenylvaleronitrile which on Grignardization likewise led to XIV:



XVII

XIV

XV heated with morpholine in a sealed tube at 150° for six hours yielded 19 per cent of XVI, which, on treatment with ethylmagnesium bromide produced XIV:



XVI

Resolutions

While DL-methadone may have been resolved in Germany (3); a description of the procedure used was not available. Brode and Hill (28), who employed D-tartaric acid in acetone, reported the first successfull[10] resolution. By adding pre-formed seeds they precipitated L-methadone-D-acid tartrate; after removing DL-methadone tartrate from the Mother liquor they regenerated the residual bases and obtained pure D-methadone by heating the residue and removing the lower melting eutectic.

Larsen, *et al.* (20), also reported a resolution of methadone via the tartrates. Howe and Sletzinger (30) treated DL-methadone with D-α-bromo-camphor-π-sulfonate in 80 per cent ethanol and precipitated the salt of D-methadone; from the Mother liquors they prepared L-methadone-D-tartrate.

DL-Isomethadone has been resolved by means of D-tartaric acid (20) and by means of p-nitrobenzoyl-L-glumatic acid in isopropyl alcohol (30).

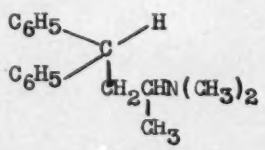
The nitrile precursors (IIIa. and IIIb) of methadone and isomethadone respectively have been resolved by means of D-tartaric acid (20, 29, 31).

It is interesting to note that in the methadone series the L-nitrile on Grignardization yields the L-ketone, while in the isomethadone series the L-nitrile leads to the D-ketone.

Reactions of Methadone (16, 32)

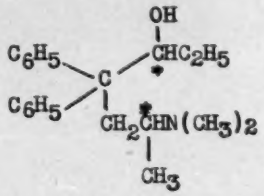
The carbonyl group of methadone has only limited reactivity, probably due to steric hindrance. Methadone forms no semicarbazone; it is not reduced by aluminium isoproproxide or the Clemmensen method or sodium amalgam or palladium and hydrogen or Raney nickel at room temperature and atmospheric pressure.[11]

Wolff-Kishner reduction (Huang-Minlon modification) of methadone causes reductive loss of the propionyl group and formation of 2-dimethylamino-4,4-diphenylbutane (XVIII). The latter is also formed when IIIa is heated with potassium hydroxide in triethylene glycol.



XVIII

Methadone is reduced catalytically in the presence of platinum or chemically by lithium aluminium hydride to the corresponding alcohol 6-dimethylamino-4,4-diphenyl-3-heptanol, known generally as methadol (XIX).



XIX

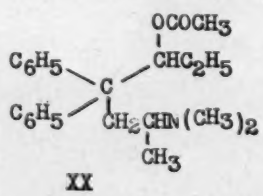
Since a new asymmetric carbon atom is produced in the course of this reduction, it would be expected that two racemic alcohols would be formed from DL-methadone. This is not the case, however. The reduction, under the conditions mentioned above, is highly stereospecific: DL-methadone leads to a single product, α-DL-methadol, in almost quantitative yield. Reduction of D-methadone yields α-L-methadol.[12] Reduction of L-methadone yields α-D-methadol.

On prolonged catalytic hydrogenation of methadone in the presence of platinum, not only the carbonyl group is reduced to hydroxyl but one of the phenyl groups is reduced to a cyclohexyl group (16).[13]

Reduction of DL-methadone with sodium and N-propanol (35, 36) is not so stereospecific as the above methods: the product consists of ca. 70 per cent of β-DL-methadol and 10 per cent of α-DL-methadol. By the same method D-methadone yields ca. 40 per cent of β-D-methadol[14] and ca. 5-10 per cent of α-L-methadol; L-methadone yields ca. 40 per cent of β-L-methadol[14] and 10 per cent of α-D-methadol.

A small amount of reductive cleavage accompanies this sodium-propanol reduction to yield 3-dimethylamino-1,1-diphenylbutane.

Methadol has been acetylated by acetic anhydride in pyridine (40 per cent yield) or by Houben's method (80-90 per cent yield) or by acetyl chloride in ethyl acetate (90 per cent yield) (16). The product, 3-acetoxy-4, 4-diphenyl-6-dimethylaminoheptane, is often referred to in the literature as acetyl-methadol (XX).



XX

[10] Thorp, Walton and Ofner (29) were unable to resolve DL-methadone by means of D-tartaric acid.

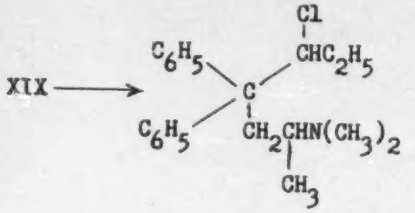
[11] Raney nickel is reported (33) to be suitable at high temperature and pressure.

[12] Note reversal of direction of rotation.

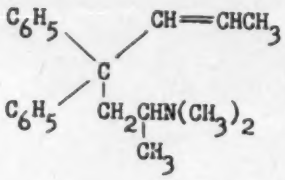
[13] The analogue of methadone in which one of the benzene rings is hydrogenated has also been prepared (34) starting with α-cyclohexyl-α-phenylacetonitrile.

[14] Note that sign of rotation is not changed.

When methadol is treated with thionyl chloride it is converted to a mixture of 3-chloro-4,4-diphenyl-6-dimethylaminoheptane (XXI) and 4,4-diphenyl-6-dimethylamino-2-heptane (XXII) representing respectively direct replacement of hydroxyl by chlorine and cleavage of the elements of water from carbons 2 and 3:



XIX → XXI

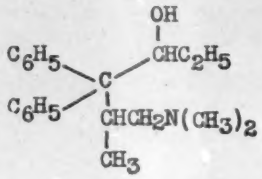


XXII

XXII is also formed from XIX by the action of phosphorus pentaoxide in toluene.

Reactions of Isomethadone (37)

The keto group of isomethadone is even more sterically hindered than the keto group of methadone. Isomethadone is not catalytically reduced in the presence of platinum. It is reduced by lithium aluminium hydride to 4,4-diphenyl-5-methyl-6-dimethylamino-3-heptanol, "isomethadol", XXIII.



XXIII

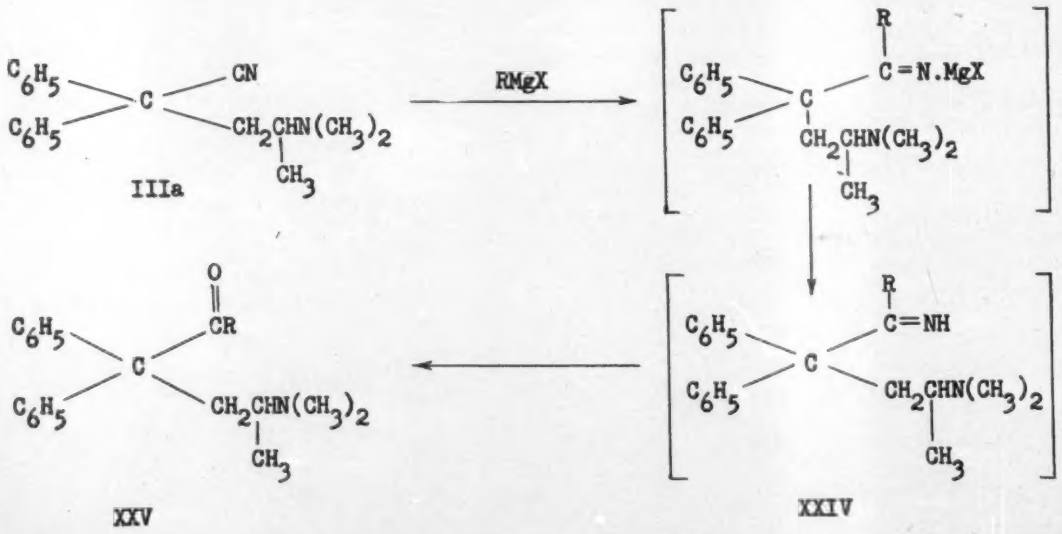
Again the reduction is stereospecific and only one-designated α- of the two possible racemates is formed from DL-isomethadone. L-isomethadone gave "α-L-isomethadol".

Sodium and propanol reduction of the isomethadones produces a mixture of α-and β-isomethadols (38).

Reactions of the Nitriles IIIa and IIIb

A number of ketones (XXV) have been prepared from the valeronitrile IIIa and the appropriate Grignard reagent. Usually the intermediate ketimine (XXIV) could not be isolated.[15]

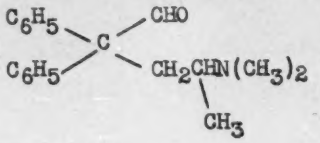
The butyronitrile IIIb on reaction with ethylmagnesium bromide yields an unusually stable ketimine (see p. 32-33. This ketimine has been acetylated (39).



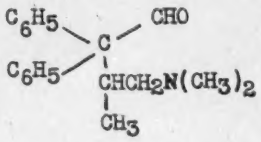
IIIa → (RMgX) → XXIV → XXV

[15] The ketimines *could* be isolated when the phenyl Grignard or isopropyl Grignard reagent was used (12). Under especially mild conditions the ketimine precursor of methadone was isolated (8b) as acetyl derivative.

Both IIIa and IIIb are reduced by lithium aluminium hydride (40) to the corresponding aldehydes (XXVIa and XXVIb):

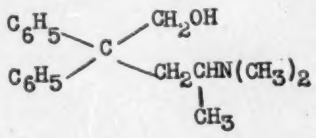


XXVIa

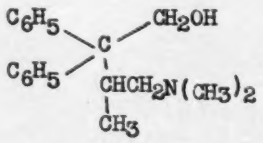


XXVIb

The aldehydes have been catalytically (PtO_2) hydrogenated to the alcohols (XXVIIa and XXVIIb):

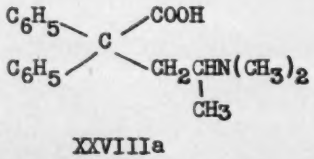


XXVIIa



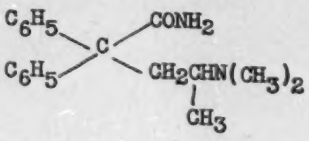
XXVIIb

XXVIIa has also been obtained by lithium aluminium hydride reduction of 2-dimethylamino-4, 4-diphenyl-valeric acid (XXVIIIa) or its ethyl ester (16).

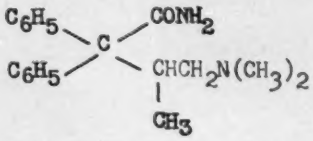


XXVIIIa

Hydrolysis of IIIa and IIIb with 90 per cent sulphuric acid (41) yields the corresponding amides (XXIXa and XXIXb),

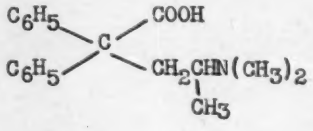


XXIXa

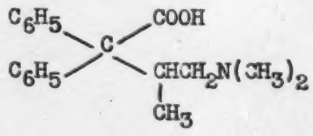


XXIXb

while hydrolysis with 72 per cent sulphuric acid for five hours at 145-150° yields the corresponding acids (16):[16]

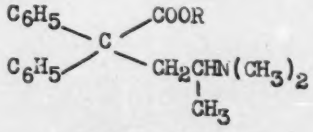


XXVIIIa



XXVIIIb

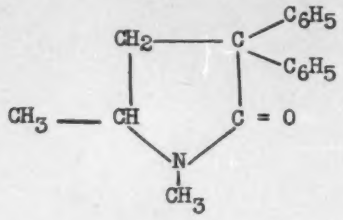
XXVIIIa (as bisulphate) treated with thionyl chloride and the with alcohols R OH (R=Me, EE, Me_2 N CH_2CH_2) yields esters (12, 42):



XXX

[16] Walton, Ofner and Thorp (12) did not succeed in hydrolyzing IIIb to XXVIIIb by sulphuric acid. Hydrobromic acid under pressure gave the pyrrolidone XXXIb. *Cf.* F. F. Blicke and A. J. Zambito, abstracts of A.C.S. Meeting, April, 1947, p. 3 K.

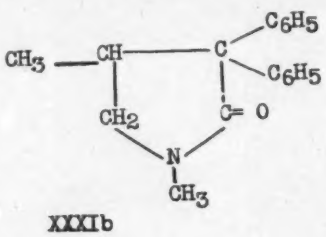
However, in attempting to form the isopropyl ester of XXVIIIa, Gardner, Easton and Stevens obtained only 5-dimethyl-3, 3-diphenyl-2-pyrrolidone, XXXIa, the same derivative obtained (12) by the action of thionyl chloride alone on the acid XXVIIIa. Similar



XXXIa

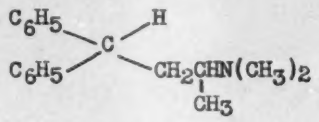
ring closures have been reported recently (43) in another connexion.

Attempts (43) to prepare esters of XXVIIIb via the acid chloride led only to the pyrrolidone XXXIb:



XXXIb

Esters of the type represented by XXX on treatment with even an excess of Grignard reagent produce ketones XXV and not *tert*-carbinols (35).

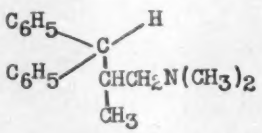


XXXIIa

The valeronitrile IIIa on treatment with sodium amide undergoes (reductive?) cleavage of the cyano-group to form 2-dimethylamino-4,4-diphenylbutane XXXIIa.

The same butane derivative is obtained by decarboxylating XXVIIIa at 200° for fifteen minutes (12).

IIIb is decyanated by the action of sodium and isopropyl alcohol (42), but not by sodium amide, to 1-dimethylamino-2-methyl-3,3-diphenyl-propane XXXIIb.



XXXIIb

References

(1) E. C. Kleiderer, J. B. Rice, V. Conquest, J. H. Williams, U.S. Dept. of Commerce, Publication Board Report PB-981, July, 1945.

(2) *J. Am. Med. Assn., 138,* 651 (1948).

(3) L. F. Small, *Ann. N.Y. Acad. Sci., 51,* 12 (1948).

(4) F. Bergel and A. L. Morrison, *Quart Rev., 2,* 369 (1948).

(5) Reference 1, p. 96A.

(6) E. M. Schultz, C. M. Robb and J. M. Sprague, *J. Am. Chem. Soc., 69,* 188 (1947); *J. Am. Chem. Soc., 69,* 2454 (1947).

(7) Private Communication to E. C. Kleiderer cited in reference 3.

(8a) N. R. Easton, J. H. Gardner and J. R. Stevens, *J. Am. Chem. Soc., 69,* 976 (1947).

(8b) N. R. Easton, J. H. Gardner, M. L. Evanick and J. R. Stevens, *J. Am. Chem. Soc., 70,* 76 (1948).

(9) M. Sletzinger and M. Tishler, U.S. Pat. 2,538,130, January 16, 1951.

(10) P. Ofner, *J. Chem. Soc., 1951,* 1800.

(11) E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc., 70,* 48 (1948).

(12) E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc., 1949,* 648.

(13) W. R. Brode and M. W. Hill, *J. Am. Chem. Soc., 69,* 724 (1947).

(14) J. Attenburrow, J. Elks, B. A. Hems and K. N. Speyer, *J. Chem. Soc., 1949,* 510.

(15) C. M. Robb and E. M. Schultz, *Org. Syn., 28,* 55 (1948); J. Mills, U.S. Patent 2,447,419, August 17, 1948; A. Homeyer and J. S. Splitter, U.S. Patent 2,443,246, June 15, 1948; D. Ginsburg and M. M. Baizer, *J. Am. Chem. Soc., 71,* 2254 (1949).

(16) M. E. Speeter, W. M. Byrd, L. C. Cheney and S. B. Binkley, *J. Am. Chem. Soc., 71,* 57 (1949).

(17) J. W. Cusic, *J. Am. Chem. Soc., 71,* 3546 (1949).

(18) R. W. Stoughton, U.S. Pat. 2,540,636, February 6, 1951.

(19) K. Pfister, U.S. Pat. 2,497,739, February 14, 1950.

(20) A. A. Larsen, F. F. Tullar, B. Elpern and J. S. Buck, *J. Am. Chem. Soc., 70,* 4194 (1948).

(21) W. B. Reid and A. W. Schneider, U.S. Pat. 2,601,323, June 24, 1952.

(22) N. R. Easton, J. H. Gardner, and J. R. Stevens, *J. Am. Chem. Soc., 69,* 2941 (1947).

(23) A. L. Morrison and H. Rinderknecht, *J. Chem. Soc., 1950,* 1478.

(24) M. Sletzinger and M. Tishler, U.S. Pat. 2,574,505, November 13, 1951.

(25) E. M. Chamberlin and M. Tishler, U.S. Patent 2,604,794, August 19, 1952.

(26) B. A. Hems and J. Elks, U.S. Pat. 2,513,173, June 27, 1950; Brit. Pat. 627,280, August 4, 1949.

(27) J. Attenburrow, J. Elks, B. A. Hems, K. N. Speyer, *J. Chem. Soc., 1949,* 510.

(28) W. R. Brode and M. W. Hill, *J. Org. Chem., 13,* 191 (1948).

(29) R. H. Thorp, E. Walton and P. Ofner, *Nature, 160,* 605 (1947).

(30) E. E. Howe and M. Sletzinger, *J. Am. Chem. Soc., 71,* 2935 (1949).

(31) A. Pohland, F. J. Marshall and T. P. Carney, *J. Am. Chem. Soc., 71,* 460 (1949).

(32) E. May and E. Mosettig, *J. Org. Chem., 13,* 459 (1948).

(33) R. L. Clark, U.S. Pat. 2,565,592, August 28, 1951.

(34) F. F. Blicke, U.S. Pat. 2,542,466, February 20, 1951.

(35) M. Bockmühl and G. Ehrhart, *Ann., 561,* 52 (1948).

(36) N. B. Eddy, E. L. May and E. Mosettig, *J. Org. Chem., 17,* 321 (1952).

(37) E. May and E. Mosettig, *J. Org. Chem., 13,* 663 (1948).

(38) E. L. May and N. B. Eddy, *J. Org. Chem., 17,* 1210 (1952).

(39) L. C. Cheney, R. R. Smith and S. B. Binkley, *J. Am. Chem. Soc., 71,* 53 (1949).

(40) M. Yandik and A. A. Larsen, *J. Am. Chem. Soc., 73,* 3534 (1951).

(41) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem., 17,* 770 (1952).

(42) J. H. Gardner, N. R. Easton and J. R. Stevens, *J. Am. Chem. Soc., 70,* 2906 (1948).

(43) P. Lucas, R. L. Clarke and A. Mooradian, U.S. Pat. 2,555,353, June 5, 1951.

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Evolution in 1951 of National Legislations on Narcotics

The Secretary-General regularly issues an *Annual Summary of Laws and Regulations relating to the Control of Narcotic Drugs*. The last summary[1] which will be published early in 1953 is based on current legislation enacted before 1 March 1952 and included in official communications received by the Secretariat between 1 June 1951 and 31 May 1952.

The legislation under consideration shows, in general, the same trends as could be observed in earlier years. Such factors as the international narcotics treaties and new scientific developments continue to dictate the course of governmental action and contribute to an ever-increasing similarity of national legislations in the field. The dependence of national legislation on international action is indicated by references to decisions of international organs placing new drugs under control or exempting preparations from control. It seems also that governments pay increasing attention to the detection, cure and rehabilitation of drug addicts.

In view of the numerous implications of narcotics control, often falling within the jurisdiction of several national government departments, interdepartmental co-ordinating and advisory committees on narcotic drugs have been set up in several countries.

Much of the recent amending legislation represents again an effort to control newly-developed synthetic substances, which continue to increase in number.

Internatonal co-operation

For the period between June 1951 and June 1952, the following changes took place in the field of international control regarding accessions, acceptances and extension of territorial application.

Israel, on 16 May 1952, acceded to the following instruments as amended by the Protocol of 11 December 1946: The International Opium Convention of 19 February 1925, the Convention of 13 July 1931 for limiting the Manufacture and Regulating the Distribution of Narcotic Drugs and the Convention of 26 June 1936 for the Suppression of the Illicit Traffic in Dangerous Drugs and also accepted the Protocol signed at Paris on 19 November 1948 bringing under international control drugs outside the scope of the Convention of 13 July 1931 as amended by the Protocol of 11 December 1946.

Japan, on 27 March 1952, accepted the Protocol of 11 December 1946 amending the international instruments on narcotic drugs and on 5 May 1952 the Paris Protocol of 19 November 1948.

Cambodia, on 3 October 1951, and Laos, on 13 July 1951, acceded to the Convention of 26 June 1936 for the Suppression of the Illicit Traffic in Dangerous Drugs.

Belgium, on 21 November 1951, accepted the Paris Protocol of 19 November 1948.

The United Kingdom, on 13 February 1952, extended to Basutoland, Bechuanaland Protectorate and Swaziland the Convention of 13 July 1931 for limiting the Manufacture and Regulating the Distribution of Narcotic Drugs.

The Secretary-General was informed of the transfer by the French Government to the Government of Cambodia of the duties and obligations arising from international sanitary conventions and was asked to note in particular the substitution of Cambodia for France in so far as concerns the application in Cambodia of the following five instruments on international narcotics control: 1912 Convention, 1925 Agreement, 1925 Convention, 1931 Convention, and 1931 Agreement.

It was reported that while the 1936 Convention has not yet been applied in Trinidad and Tobago all the offences specified in article 2 thereof are punishable in the territory.

The Government of Italy reported that the rules of the international conventions are applied in the Trust Territory of Somaliland.

The Government of the United States of America stated that the international regulations relating to narcotics are followed in practice in the Trust Territory of the Pacific Islands.

The Economic and Social Council, at its fourteenth session, noting that the use of synthetic narcotic drugs was developing rapidly, drew the attention of governments in particular to the desirability, should they not already have done so, of bringing all synthetic drugs under their national legislation as soon as they appear, and of making regulations to ensure that all packages containing a synthetic narcotic drug should be clearly marked with a double red line so that they may be promptly identified by the competent services.

[1] See document E/NL.1951/Summary.

To date the following synthetic drugs are controlled by virtue of the application of the 1948 Protocol: pethidine, bemidone, keto-bemidone, nisentil, methadone, iso-methadone, phenadoxone, NU-1779, NU-1932, NU-2206, N.I.H.-2933, N.I.H.-2953, 3-methoxy-N-methylmorphinan, and their respective salts. As regards natural drugs, dihydrocodeine, acetyldihydrocodeine and their respective salts come under the 1948 Protocol.

The Narcotic Drugs Commission, formed within the framework of collaboration in the field of public health in Benelux, studied ways and means to obtain the highest possible degree of uniformity in narcotics legislation as well as in the list of controlled narcotic drugs. It was decided to adopt, in the Netherlands and in Luxembourg, the system used in Belgium for ordering narcotic drugs. As a result there will be, in each of the three countries, a centralized administrative control over all deliveries by wholesale-dealers and manufacturers and over the reports of pharmacists and physicians. Although the 1948 Protocol has not yet been accepted by all three countries, it was decided that they would, in principle, institute supervision of the narcotic drugs to which the Protocol applies. It was also reported that it was the intention of the Benelux authorities in the future, when intra-Benelux-trade will no longer be considered as import and export, to keep regular contact regarding the import and manufacture of narcotic drugs in order to avoid that the total estimates, established in accordance with the 1931 Convention, be exceeded.

On 26 August 1950, the Political Committee of the League of Arab States created a Permanent Anti-Narcotics Bureau empowered to put forward to the governments concerned "proposals for the consolidation and enforcement of the legislative and administrative measures to be taken" in respect of the production and smuggling of narcotics. The report on the first year of the Bureau's operations stated that a new law on narcotics control was about to be drawn up in Saudi Arabia; the hope was also expressed that the ratification of the Egyptian-Lebanese commercial treaty would encourage Lebanese cultivators to substitute fruit cultivation for the growing of hashish, while it was noted at the same time that Syrian cultivators have started growing cotton instead of hashish.

Scope of control

The Government of France stated that — as the League of Nations had recommended that no new licences for the manufacture of narcotic drugs be issued if the existing factories were able to meet demand; as it was practically impossible to control the manufacture of synthetics due to the fact that they are prepared from raw materials commonly use in industry; as it would be difficult to permit the manufacture of some, while prohibiting the manufacture of other synthetic drugs; and as the appearance of a great number of these products on the market might not give the medical profession time to acquaint itself with their effects — the following policy had been adopted: all synthetic narcotic drugs appearing on the world market are automatically placed on France's schedule of narcotic drugs (schedule B). In accordance with the provisions of the decree of 19 November 1948, anyone wishing to put such a product on the French market must apply for an authorization from the Ministry of Public Health and Population, and no authorizations are granted for either domestic manufacture or import. The only synthetic which may be manufactured in France is pethidine.

In 1950 the Central Government's narcotics legislation was extended so as to apply throughout all of India.[2]

In New Zealand the Dangerous Drugs Regulations of 1951 primarily consolidate the existing provisions governing licences, records, prescriptions and the supply and possession of narcotic drugs.

In 1951 Switzerland passed a new narcotics law, which entered into force on 1 June 1952. This law controls categories of drugs by definition and appoints the Federal Health Service as the authority responsible for drawing up a detailed schedule of controlled drugs and preparations. The substances controlled are listed as follows: opium; poppy straw used for the production of narcotic substances; coca leaf; "hemp"; the phenanthrene alkaloids of opium and their derivatives, ecgonine and its derivatives, and the respective salts of these substances which give rise to addiction; the resin of the glandular fibres of the hemp plant; any other substance capable of producing addiction and of causing harmful effects similar to those of morphine, cocaine, and "hashish"; and all preparations containing any of the above substances. The Federal Council may, moreover, place under control substances which, while not themselves addiction-producing, may be converted into such substances. The Council may exempt from the scope of the law — either partially or entirely — any substances in quantities or concentrations which cannot give rise to addiction, provided that they cannot practicably be recovered or converted into other addiction-producing substances. Substances which do not come within the above definition of narcotics but which are of analogous chemical composition and are likely to produce similar effects may not be used, manufactured, or imported for commercial purposes except with the express consent of the Federal Health Service and in accordance with the conditions it may prescribe; such an authorization being valid until the Health Service determines whether or not the substance is to be classified as a narcotic.

The law prohibits the importation or manufacture of, and the trade in, prepared opium and opium dross

[2] This legislation does not extent to Jammu and Kashmir.

(*déchets*); diacetylmorphine and its salts; and preparations containing any of these substances. It also prohibits the issue to the public of "hashish", defined as the resin of the glandular fibres of hemp. The Federal Council is empowered to prohibit the importation or manufacture of, and the trade in, other narcotic substances the manufacture of which the international conventions may forbid, or the principal manufacturing countries may forego. It may, to comply with the conventions, forbid authorized narcotics manufacturers and narcotics dealers to manufacture, import, export or store certain narcotic substances, or impose quantitative restrictions, powers which the Council may delegate to the Department of the Interior. Any existing stocks of prohibited narcotics are to be converted into substances authorized by law, the conversion to take place under the supervision of the cantonal authorities. Narcotics which cannot be converted are to be destroyed. The Federal Health Service may, however, authorize the use of any prohibited substance except "hashish" for scientific purposes.

The United Kingdom consolidated its narcotics legislation by issuing a new Dangerous Drugs Act, which entered into operation on 1 January 1952. The Act covers the importation, exportation, manufacture of and trade in narcotics in Great Britain and Northern Ireland.

In 1951 the Governor of Gibraltar was given express powers to enact rules for controlling or restricting the production, possession, sale and distribution of raw opium, coca leaves, and Indian hemp and to fix such penalties for the breach or non-observance of these rules as he might think fit, not exceeding however, a maximum of one month's imprisonment or a fine of £150. Previously only the export and import of these substances had been prohibited. New rules were issued accordingly, prohibiting their possession.

In Singapore a new Dangerous Drugs Ordinance and Regulations under that Ordinance entered into force on 1 March 1951.

Purposes of control

The purpose of all narcotic control is the limitation of narcotic drugs to medical and scientific uses. In their efforts to clarify what constitutes medical and scientific use of narcotic drugs, governments now frequently limit the practitioner's discretion, e.g., by prohibiting altogether the use of certain substances, most frequently diacetylmorphine (Switzerland); by establishing by law the maximum amounts which may be prescribed at one time in the treatment of diseases (New Zealand); or by establishing by law the maximum doses which may be administered for the treatment of addiction (California).

Swiss federal legislation, while containing no dosage limitations or similar restrictions, states expressly that dentists, physicians, and veterinarians may use (and the latter two categories, prescribe) narcotic drugs only within the limits permitted by science. The cantons are, however, entitled to limit dentists to the use of specific narcotics. In the United States, California legislation which, as noted above, does contain restrictions regarding a physician's use of drugs, contains, in addition, a provision stating expressly that a physician may prescribe, furnish, or administer narcotics only in such quantities and for such length of time as are reasonably necessary.

Prohibition of non-medical use of opium

While the struggle for the abolition of opium smoking, specially in certain countries of the Far East, has been waged by enforcement authorities through stringent action against opium dens and smuggling, significant legislative provisions have been issued more particularly in Burma, India, Pakistan, and Singapore.

In Burma, according to the annual report for 1950, it has been proposed to extend the suppression of the Opium Dens Act, 1950, to other towns in the Union of Burma besides Rangoon; action has been kept pending, however, until the anti-opium clinics are opened for operation. Moreover, the Government of the Union of Burma reported that towards the end of 1950 it established an Opium Enquiry Committee which was to review the existing opium policy in the country.

The Government of India reported that in twenty-five out of twenty-seven states constituting the Indian Union, laws are in force controlling opium-smoking; out of these twenty-six states, six prohibit opium-smoking completely, while the others have adopted a policy of gradual suppression.

While opium-smoking was reported to be prohibited in Pakistan (excepting being made for existing addicts on medical grounds), the Government of Pakistan, nevertheless, issued a directive on 24 May 1950 to the provincial governments and to the federated states to consider and to adopt more stringent measures to ensure complete prohibition of opium-smoking without any exception.

The new Dangerous Drugs Ordinance of Singapore repeals the Opium and Chandu Proclamation of 1946 and includes, instead, provisions prohibiting the import, export, possession, manufacture, and sale or other dealings in, as well as use of, prepared opium.

Domestic trade

The establishment of a central office for the manufacture and distribution of medicinal narcotic drugs is reported by the Chinese Government.

The new consolidated narcotics legislation of New Zealand, the United Kingdom, and the United Kingdom's colony of Singapore, as well as the narcotics law of Switzerland all distinguish between general

licensing by virtue of a profession (applicable usually to members of the medical profession and pharmacists) and individual licensing (applicable to wholesalers, etc.).

Official prescription blanks for narcotic substances are required by the Union of Soviet Socialist Republics and by the state of California in the United States. The special counterfoil books required in Metropolitan France are also reported obligatory in Madagascar.

In the Cameroons under French administration and in Singapore, advertising for narcotic substances is subject to licensing provisions under the narcotics laws.

Turkey again permitted middlemen to purchase opium from the cultivators provided they delivered it to the Agricultural Products Office or its agency.

* * *

Provisions relating to the production of raw materials and the manufacture of narcotic drugs as well as measures intended to improve the existing machinery of records, reports and governmental inspection, penal sanctions which various countries enacted for the suppression of the illicit traffic in narcotic drugs, and measures relating to the administrative organization of the control of narcotic drugs at the national level, are dealt with in other chapters of the Annual Summary of Laws and Regulations.

Legal Trade in Narcotics in 1951

During its sixteenth session, the Economic and Social Council, which is meeting in June 1953, will examine the report of the Permanent Central Opium Board on the task accomplished in 1952.[1] This report presents an over-all picture for 1951 of the production and consumption of narcotics, and of their illicit traffic throughout the world, as it is shown by the analysis of the statistics submitted to the Board by governments.

The reader will find below the main features included in the report of the Permanent Central Board.

Present state of control

The object of the control over the licit movement of narcotic drugs exercised by the Board by virtue of international conventions is to prevent licitly produced substances of this nature from being diverted to illicit ends. The statistics which governments are required to supply under the above conventions are accordingly scrutinized, quarter-by-quarter, with a view to verifying whether all narcotic drugs exported from one country to another duly arrive at their destination. In addition, the Board draws up, for each country and each substance, an annual balance-sheet of the quantities available and quantities utilized, so as to determine the balance available at the end of the year, which should correspond to the stocks declared by governments. The control also aims at ensuring that supplies (imported or manufactured) are kept within the limits, calculated in accordance with the provisions of the 1931 Convention, on the basis of the estimates provided for therein.

As regards the first aspect of this control, *viz.*, international trade, the Board had, since its previous report, undertaken 106 investigations, of which sixty-one had been completed at the time of writing the report. They revealed no disappearances of narcotics, but only statistical errors or omissions.

The Board came to the conclusion that, in general, replies from governments have been prompt and that, in most cases, they provided all the information necessary for a decision on the case in question.

As will be clear from the above, the Board's control is very largely based on the statistics which governments have to supply under the terms of the international conventions on narcotic drugs. In all, the Board received 90 per cent of the statistical returns required for 1951.

[1] For the report of the Permanent Central Opium Board on its work in 1951, see *Bulletin on Narcotics*, vol. IV, No. 2.

At the time of writing the report, all the principal countries in which raw opium is licitly produced had declared figures which purport to represent the quantity so produced, but which in some cases represent only the quantities taken into possession by government agencies. The statistics for countries manufacturing narcotic drugs were nearly complete: only from one of such country, and that not the most important, was the required information still outstanding. As regards coca leaves, on the other hand, the position was still far from satisfactory: to the Board's knowledge, these leaves are produced in four countries, of which the two most important had not supplied the information which the Board would wish to have.

In its last report the Board stated that the figure given by the Iranian Government for the stock of raw opium in hand at 31 December 1950 was 256 tons, whereas, according to the Board's calculations, based on the Iranian statistics, it should have amounted to 589 tons, which would imply that 333 tons of raw opium had disappeared during the year. The report went on to say that the Board had drawn the attention of the Government of Iran to the matter in a letter dated 8 August 1951, but that no reply had been received.

The explanation requested was supplied by the Iranian Government in a letter dated 14 April 1952, which represented that the apparent discrepancy was due, first, to the fact that exports had in reality amounted to 240 tons, and not to 43 tons as previously reported to the Board, and secondly, that the year's supply of raw opium (632 tons) had been reduced by 135 tons as a result of dryage and losses incurred in manipulation. As regards exports, the Board confirm that the figure of 240 tons agrees with importing countries' declarations.

No sooner had this explanation been received than another discrepancy arose — this time in connexion with the stock of opium in hand on 31 December 1951. This, according to the Iranian Government's statement amounted to 225 tons (*viz.*, 49 tons of raw opium and 176 tons of opium processed for export), whereas, according to the Board's calculations, based on the Iranian statistics, it should have amounted only to 22.8 tons. The Board wrote to the Government of Iran on the subject on 22 September 1952 but no reply had been received at the time of writing the report.

The Board was informed that considerable quantities of opium from Jehol had been offered for sale

by the Government of the People's Republic of China. So far as the Board was aware, this was the first time that Chinese opium had been offered for sale on the licit market.

The Board therefore addressed the following letter, dated 6 November 1951, to the Minister for Foreign Affairs of the People's Republic of China:

"I have the honour to inform you that the attention of the Permanent Central Opium Board has been drawn to the fact that 500 tons of opium at present in China were offered for sale in Hong Kong.

"The Board, therefore, has requested me to ask you to be so good as to inform it of the origin of this opium, the period in which it was collected, the total stocks of opium at present in China, and whether the cultivation of the opium poppy and the export of the opium are still prohibited in China."

No reply was received to the above letter, but the Division of Narcotic Drugs of the United Nations Secretariat supplied the Board with the text of a circular order of the State Administrative Council of the Central People's Government of the People's Republic of China, dated 24 February 1950. This circular order provides, amongst other things, for the prohibition, as from the date of its issue, of the production and sale of opium and narcotic drugs throughout the country. It therefore answers one of the questions raised by the Board, the other questions remaining unanswered however.

In its last report, the Board mentioned that considerable quantities of diacetylmorphine had been diverted from the licit to the illicit market, and that it had, in consequence, asked the Italian Government "that the stocks of diacetylmorphine held by manufacturers and wholesalers should be limited to an amount representing licit requirements for about eighteen months; that any surplus stock should be kept under the direct supervision of the Government; and that no new production should take place until this stock has fallen to the above-mentioned level".

The Italian Government informed the Board that the manufacture of this drug has been suspended in 1951 until further notice. At that time, it amounted to 50 kg., whereas, in the three previous years, it had averaged 235 kg. a year. Stocks had, moreover, fallen from 204 kg. in 1949 to 142 kg. in 1950 and 78 kg. in 1951, the latter figure representing an estimated 18-months' consumption.

The Italian Government also announced that the High Commissioner's Office for Hygiene and Public Health was carrying into effect a new law on narcotic drugs, and that the action taken to supervise and control the production of and trade in those drugs had made it possible to "... discover and strike at the source of supply of the Italian-American organization which in recent years has acquired and disposed of large quantities of heroin".

The Board expressed the hope that this strengthening of control in Italy would prevent a repetition of such leakages into the illicit traffic.

In the course of the correspondence referred to in the foregoing paragraph, the Italian Government indicated that the illicit traffic in diacetylmorphine, discovered in Italy, had ramifications in the Free Territory of Trieste. The authorities of the Anglo-American Zone in this territory made an investigation which confirmed the existence of such ramifications and resulted in seizures of narcotics and in the arrest of a certain number of traffickers.

The question of diacetylmorphine

Throughout their tenure of office, the present Board and the Supervisory Body had been greatly exercised by the very high consumption of diacetylmorphine in certain countries. It will be recalled that the 1931 Conference recommended that the use of this particularly dangerous drug should be restricted or abolished. They had repeatedly called the attention of governments to the persistent widespread recourse to diacetylmorphine despite this recommendation and had pressed for the adoption of measures which would reduce its consumption; the Board's report for 1948 and the Supervisory Body's statement of estimates for 1949 contained the following phrase:

"The present report is being communicated to the World Health Organization, and the Permanent Central Opium Board and the Supervisory Body call the attention of the Organization to the views they have expressed on the present use of diacetylmorphine and the problems in medical practice which it raises."

The following table sets out the consumption, per million inhabitants during the past six years, in the countries to which the Board and the Supervisory Body had particularly directed their attention in this respect:

Consumption of diacetylmorphine per million inhabitants

Kilogrammes

Country	*1946*	*1947*	*1948*	*1949*	*1950*	*1951*
Finland	25.54	17.67	38.15	16.93	5.2	4.49
Italy	2.71	5	4.26	4.16	2.31	2.21
New Zealand	4.54	3.33	2.72	2.13	1.04	2.06
Sweden	2.83	4.12	1.88	2.02	2.29	2.41
Australia	2.42	3.3	4.68	4.3	4.52	5.25
United Kingdom .	1.91	1.87	2.18	2.71	2.27	2.38

The Board and the Supervisory Body were gratified to observe that as a result of these efforts there is a general trend towards lower consumption. In Australia, where consumption has increased, the Government is making a thorough enquiry into the reasons for this phenomenon.

Even more important is the growing inclination of governments to prohibit the use and manufacture of

this drug. In 1951, no less than fifty States reported to the World Health Organization that they had discontinued, or declared their willingness to discontinue, its medical use, a state of affairs which represents a considerable advance since the year 1949, when only twenty-four countries had stopped such use. This trend happily continues. In Sweden the manufacture of diacetylmorphine was discontinued as from 1 January 1952, and there is good reason to hope that consumption in this country will presently cease altogether. In Switzerland also, manufacture of and trade in this drug have lately been prohibited; and in the Union of South Africa, Switzerland and a number of Non-Self-Governing Territories its use has been forbidden.

This problem continues to engage the full attention of the Board and the Supervisory Body, who are following up their action in this field in close collaboration with the World Health Organization.

Conversion of codeine into morphine

The Board learnt that, in 1951 and for the first time, codeine had been converted into morphine. The government which reported this operation announced that 26 kg. of codeine had been used to produce 18 kg. of morphine, which is equivalent to a yield of about 70 per cent.

The Board was not in a position to tell how this conversion process was likely to develop in the future and whether, in consequence, some change may be called for in the control exercised over codeine under the 1931 Convention.

Narcotic drugs covered by the Protocol of 1948

In its last report, the Board referred to certain problems raised by the discovery of new synthetic and other narcotic drugs and listed for the consideration of governments a number of measures calculated to guard against the improper use of such drugs. It was gratified to learn that, on 27 May 1952, the Economic and Social Council requested the Secretary-General to draw the attention of governments to the desirability of putting these recommendations into effect.

A new synthetic drug, 3-methoxy-N-methyl-morphinan and its salts, together with the salts of all the substances previously brought within the scope of the Protocol of 19 November 1948, were likewise brought under control during the current year. Thus, at the present time, sixteen narcotic drugs, their salts and the preparations made therefrom are subject to international control in virtue of the provisions of the 1931 Convention, while fifteen others and their salts are made amenable to the same control under the provisions of the Protocol of 1948.

Trends in the licit movement of narcotic drugs during 1951

A. Raw materials

(1) *Opium.* The principal countries with licit production of opium — India, Turkey, Iran, USSR and Yugoslavia — supplied the Board with statistics under the headings prescribed by the 1925 Convention; the figures for only two countries were missing, and these are in any case countries of much less importance as opium producers — namely Laos and Vietnam.

According to these statistics, the following amounts of raw opium were produced during the years 1947-1951:

Production of raw opium

	1947	*1948*	*1949*	*1950*	*1951*
			(tons)		
India	429.7	342.2	220	230.7	526.7
Turkey	302.7	380.2	10.4	184.8	357.8
Iran	3.5	21.3	199.7	480.9	32.2
USSR	73	75	76	85.7	93.8
Yugoslavia	23.4	21.5	0.5	19.2	22
Bulgaria	3.4	4.4	0.7	1	0.9
Laos and Vietnam	?	?	?	?	?
Other countries	0.1	0.1	–	0.5	–
Total (incomplete)	835.8	844.7	507.3	1002.8	1033.4

The Board had certain reservations to make regarding the figures given above. Several of them, in fact, represent not actual production but only the amounts bought from producers by the State monopolies, and their significance depends not only on the efficiency of the control exercised in the country in question but also to a large extent on the amount of the total quantity harvested which the government agencies decide to acquire. The variations occurring from year to year are involuntary rather than deliberate in so far as they depend on weather conditions.

All the leading producing countries had supplied the Board with information in regard to the utilization of their opium. The fact, however, that the moisture content — and hence the weight — of opium changes considerably during storage greatly impairs the effectiveness of statistical control. To improve matters in this respect the national authorities should, if they are not already doing so, determine the moisture content when the opium is first acquired, while it is in stock and when it passes into utilization or export, and should declare such figures to the Board. This would enable the Board to determine the degree to which the statistics relating to production, consumption, exports and stocks are truly comparable.

The most accurate statistics supplied by opium-producing countries to the Board are those relating to exports, these transactions being easier to control than are production and consumption. Moreover, as the importing countries declare their imports, the Board can ask for explanations of any discrepancy which arises between export and import figures.

The opium exported to manufacturing countries by the producing countries does not represent all the raw material available for the manufacture of morphine. Several countries use their own opium for this purpose, others use poppy straw. Exports of opium to manufacturing countries show a very sharp rise during the last two years, and were 50 per cent greater in 1951 than in 1939, the pre-war record year.

For three years, India has been the only producing country exporting opium licitly to countries (Pakistan and Ceylon) where it is utilized for purposes which are described as quasi-medical. Such consumption exists also in India itself and there is non-medical consumption in Cambodia, in Laos and Vietnam, where it is met out of domestic production, and in Thailand, where it seems to have been met for several years out of opium confiscated in the illicit traffic.

In 1951, as in the years 1947-1950, most of the non-producing countries importing opium for purposes of alkaloid extraction, as well as those where it is used for other than medical purposes, duly rendered an account of the amounts supplied to them by producing countries.

(2) *Poppy straw.* This raw material for the extraction of morphine is not covered by the International Conventions on Narcotic Drugs. Most of the countries using it, however, notify the Board of the amounts used in manufacture and the amounts of morphine thus produced. In certain countries, the whole poppy is used, in others only the capsule, which is richer in morphine, and the yield varies accordingly.

In 1951, 11.6 tons of morphine were manufactured from poppy straw; this figure is incomplete since the statistics for Czechoslovakia were not received. Assuming that manufacture in that country was the same in 1951 as in 1950, the world total for 1951 would be 12.4 tons, the highest so far recorded. In 1947, the amount manufactured was only 4.6 tons and the increase is largely due to production in Hungary, which rose from 0.8 ton to 6.6 tons in 1951, and in Germany, where it rose from 0.5 ton to 3.2 tons during this period. By comparison with the pre-war figure (1.8 tons in 1937), the amount of morphine thus manufactured has increased sixfold.

In 1951, the manufacture of morphine from poppy straw represented 16 per cent of the total morphine manufacture; in 1947, it represented only 4.4 per cent.

(3) *Coca leaves.* The Board stated that, so far as its knowledge goes, coca leaves are produced in four countries: Bolivia, Colombia, Indonesia and Peru.

Only Colombia and Indonesia, which are not the largest producers, send the Board figures of their production, which, in 1951, amounted to 203 tons in Colombia and 4 tons in Indonesia. These two countries have also accounted for the quantities so produced; in Colombia, the leaves are chewed by the indigenous population, while those produced in Indonesia are exported to countries manufacturing cocaine.

The other two producing countries, Bolivia and Peru, have never sent statistics of their production to the Board; the only information they ordinarily supply relates solely to exports. These countries produce very large quantities of coca leaves, of which the greater part are chewed within the country, while some are exported for that purpose and for the manufacture of cocaine and of non-narcotic coca-flavoured beverages. Moreover, in Peru, coca leaves are also used for the manufacture of crude cocaine which is subsequently exported; since 1949, however, the Peruvian Government has not been supplying statistics in respect of such manufacture. Such wide gaps in the supply of statistical material render impossible, in respect of this product, the control which the 1925 Convention was designed to secure.

It is relevant to recall, says the Board, that the Expert Committee on Drugs Liable to Produce Addiction, of the World Health Organization, has recorded its view that "coca chewing comes so closely to the characteristics of addiction... that it must be defined and treated as an addiction, in spite of the occasional absences of some of those characteristics". The practice has been the subject of careful study by the Economic and Social Council and its Commission on Narcotic Drugs for some time past and it still engages their close attention.

For coca leaves as for opium, the fullest statistics furnished by producing countries are those of exports.

The situation during the years 1947-1951 calls for the following comments:

(i) The quantities of coca leaves exported to cocaine-manufacturing countries do not represent all the raw material made available to them for the manufacture of cocaine, for Peru also supplies them with crude cocaine. In the last five years these deliveries have been as follows (kilogrammes):

1947	*1948*	*1949*	*1950*	*1951*
863	1,276	383	315	134

(It can be estimated roughly that 1 kg. of crude cocaine yields as much cocaine as 200 kg. of coca leaves.)

(ii) Since 1947, no coca leaves have been used in the United States of America for the preparation of non-narcotic coca-flavoured beverages.

(iii) Argentina is the only non-producing country which imports coca leaves for chewing and all the leaves exported thereto in 1951 (154 tons) were, as in previous years, intended for this purpose.

Most of the countries which import coca leaf have duly rendered an account of their imports in 1951 as in previous years.

(4) *Indian hemp.* This plant is of course principally used for the manufacture of cordage. It also is the

basis of certain medicinal preparations, which are not widely used (some 600 kg. a year), and which present no important problem; and it is the source of non-medicinal substances which are consumed by addicts in several parts of the world under various names such as hashish, marihuana, charas and ganja, and which are the object of an extensive illicit traffic. The statistics to be supplied to the Board under the Convention of 1925 relate only to licit imports, exports, confiscations effected on account of illicit imports and exports, plus, in respect of medicinal preparations, the licit consumption and stocks. Having regard to the fact that such information can, in the circumstances, depict only a very small part of the various operations, licit or illicit, carried out in respect whether of the raw materials or the products derived therefrom, the Board felt unable to comment on it.

B. Manufactured drugs

(1) *Morphine.* In 1951, world manufacture of morphine reached a new record total of 72 tons. This excludes production in Czechoslovakia, which had not submitted figures but which, in the preceding year, had an output of 0.8 ton. The highest total previously attained was 65 tons in 1950. All the main manufacturing countries contributed to the increase, with the exception of the United States of America and the Federal Republic of Germany, where production fell by 3.8 tons and 0.6 ton respectively.

There has, in fact, been a steady increase in the annual output of this drug since the end of the Second World War. The pre-war record figure was 55 tons, which was achieved in 1929.

No less than 85 per cent of the morphine manufactured is subsequently converted into codeine, so that it is the demand for codeine which governs the manufacture of morphine, and it is the increase in that demand which accounts for the continuing expansion of such manufacture.

Morphine is also converted into other drugs such as diacetylmorphine, dionine, dihydromorphinone and products not covered by the international conventions; and such conversion into these products generally absorbs about 10 per cent of the morphine manufactured.

It follows that the amount of morphine remaining available for use as such represents only 5 per cent of the total quantity manufactured.

(2) *Diacetylmorphine.* In 1951, diacetylmorphine was manufactured in seven countries, which together produced 381 kg. of this substance. They are, in order of volume of production, the United Kingdom (278 kg.), Italy (50 kg.), Sweden (19 kg.), Belgium (13 kg.), France (8 kg.), Argentina (7 kg.), and Germany (6 kg.).

World manufacture of this drug has declined substantially since 1929, when international control was first applied. In that year, it amounted to 3,621 kg., falling to 1,315 kg. in 1932, to 851 kg. in 1937, to 581 kg. in 1947, to 450 kg. in 1950 and, as already related, to 381 kg. in 1951. The latest drop in the world total is particularly gratifying, being due to a reduction of manufacture in Italy from 209 kg. to 50 kg., as explained above.

The number of countries manufacturing diacetylmorphine has also fallen: before the war there were sixteen; in 1951 there were only seven. The countries which have stopped manufacturing this drug are Czechoslovakia, Finland, Hungary, Japan, the Netherlands, Switzerland, the USSR and Yugoslavia; in regard to one former manufacturing country, Korea, the Board had no information for 1951.

(3) *Dihydrohydroxycodeinone, dihydrocodeinone, dihydromorphinone and acetyldihydrocodeinone.* Production of these drugs rose from 587 kg. in 1947 to 966 kg. in 1948 but subsequently registered a slight decline. However, in 1951, it was still twice as high as before the Second World War.

(4) *Codeine.* From the point of view both of the amount manufactured and the amount consumed, codeine is the most important chemical derivative of opium. In 1934, the first year for which statistics concerning this drug are available, 17.2 tons were manufactured. Production has increased almost four-fold since then and, in 1951, reached a total of 65.4 tons. All the main manufacturing countries contributed to the increase in production.

It has been shown that the manufacture of codeine absorbs 85 per cent of the morphine now manufactured; in terms of opium, 65 per cent of the last five years' licit production has ultimately gone to produce codeine. This latter percentage has risen as a result of the substantial decline which has already taken place in the accepted non-medical use of opium; as this decline continues, the licit demand for opium will increasingly be governed by the need for codeine.

As already mentioned, a reconversion of codeine into morphine was accomplished for the first time in 1951, but this operation did not involve any large quantities: 26 kg. of codeine, yielding 18 kg. of morphine.

(5) *Dionine.* Production of dionine, though only a tenth of that of codeine, shows a similar trend and in 1951 reached a record figure (5.9 tons).

(6) *Crude cocaine.* Except for the few kilogrammes produced in France and Switzerland in 1951, crude cocaine is now extracted only in Peru, whence it is exported to cocaine-manufacturing countries. Peru has furnished no production statistics for the last two years, the only figures supplied being those for exports. The latter are on the decline, having fallen from 863 kg. in 1947 to 134 kg. in 1951. The number of importing countries is likewise on the decline: seven in 1947, one only in 1951.

(7) *Cocaine.* Production of this drug has remained stable since 1948 at about 1.5 tons. This represents a considerable reduction by comparison with the pre-war figure.

(8) *Synthetic narcotic drugs.* Not until March 1951 were synthetic drugs brought under international control in virtue of the Protocol of 1948. In several countries, however, certain of these drugs had already been subject for some years to the control applying to drugs covered by the 1931 Convention and were included by those countries in their statistics. There are a dozen drugs at present. The use of one of them, pethidine, has developed very rapidly and is still expanding. The use of methadone shows a tendency to become stabilized; that of other more recently discovered drugs (phenadoxone, racemorphan, levorphan, for example) is only beginning and the Board had very few statistics regarding them.

The main manufacturing countries (France, Germany, the Netherlands, the United Kingdom and the United States of America) have declared their pethidine production for 1949, 1950 and 1951, which totalled 6,660 kg. in 1949, 7,400 kg. in 1950, and 11,400 kg. in 1951. As can be seen, there has been a rapid increase in the demand for this drug (70 per cent in three years). The other countries which, there is reason to believe, produced pethidine during the years in question are Hungary, Italy, Switzerland and the Union of Soviet Socialist Republics. In the case of Italy, only the years 1949 and 1950 are in doubt as this country declared a production of 738 kg. of the drug in 1951.

The United Kingdom and the United States of America were the only countries to declare the amount of methadone manufactured during the three years in question — *viz.*, a total of 210 kg. in 1949, 510 kg. in 1950 and 428 kg. in 1951.

Summary

The position with regard to substances generally considered as raw materials is still very unsatisfactory.

The total licit world production of raw opium is not accurately known and that of coca leaves cannot even be conjectured. On the other hand, the statistics relating to the use of these substances for medical and scientific purposes (i.e., manufacture of their chemical derivatives) are almost complete. The same is true of the licit use of opium for non-medical purposes, though figures for coca leaf similarly used are almost entirely lacking. Accordingly, in reviewing the recent history of these substances, the only general trends which can be distinguished with any assurance are the following:

(*a*) Since the end of the Second World War, the reported licit production of opium shows a decline by comparison with the pre-war figures. This decline is explained by a falling-off in the licit use of opium for non-medical purposes; it is, however, partly offset by the steady increase in demand for medical and scientific purposes (manufacture of chemical derivatives such as morphine and codeine);

(*b*) The demand for coca leaves for medical and scientific purposes (cocaine extraction) has varied from year to year since 1947 but shows a falling-off by comparison with the figures for the period before the Second World War. It is only a fraction of the licit demand for non-medical uses;

(*c*) Generally speaking, the countries in which these raw materials are used for medical and scientific purposes render due accounts thereof.

With regard to Indian hemp and its preparations, as the statistics supplied to the Board under the 1925 Convention cover only some of the economic processes relating to these substances, the Board was unable to draw any conclusions from them.

As far as manufactured drugs are concerned, the position is as follows:

(*a*) Production of codeine (the largest in point of volume) is on the increase; and the same is true of dionine. Total production of morphine shows a similar tendency, the bulk of it (90 per cent) being used for the production of the two previously mentioned drugs. On the other hand, the amount of morphine produced for direct use tends to fall. Production of cocaine is stable, while that of diacetylmorphine shows a marked decline.

(*b*) The Board had only very incomplete information in regard to the narcotic drugs covered by the 1948 Protocol, except perhaps as regards pethidine, the statistics for which are already fairly complete and serve to show a considerable and rapid increase in production.

(*c*) It is still too early to judge how far the use of the chemical derivatives of opium may be reduced by increasing recourse to synthetic drugs; so far their consumption, taken as a whole, shows no sign of a decline.

Most countries have declared full particulars of their dealings in narcotic drugs in 1951 and the Board considered that due account of the drugs so dealt in has been rendered. The Board repeated, however, that it finds it difficult, if not impossible, to carry out a similar verification in respect of the opium and the coca leaves available in the producing countries.

Conclusions

To sum up, the Board felt that the matters related in the body of this report suggest certain conclusions which invite general concern. The most outstanding are:

(*a*) The vagueness which characterizes the statistics of the principal opium-producing countries;

(*b*) The impossibility of determining the licit production of coca leaves;

(*c*) The increase in the number of narcotic drugs, which has almost doubled in the last five years;

(*d*) The steady and remarkable increase in the consumption of codeine during the last two decades;

(*e*) The ever-wider use of synthetic narcotic drugs without any significant decline in the use of the chemical derivatives of opium.

United Nations Documents Dealing with Narcotic Drugs

A list of the more important United Nations documents relating to narcotic drugs is given in the following pages. These documents contain a variety of information, legal, technical, administrative and the like.

Documents that were merely ephemeral have been omitted. The selection was made to help the research worker and it may not be above criticism. Since most of the documents belong to a strictly defined category, it was thought preferable to avoid multiple references which would make the list unwieldy.

It is hoped that, such as it is, this list will be useful. All documents can be consulted either at the Permanent Headquarters of the United Nations, or at the United Nations Library in Geneva.

The documents are classified as follows:

I. Raw materials and derivatives
   - A. Opium and derivatives
   - B. Coca leaf and derivatives
   - C. Indian hemp and derivatives

II. Trade in narcotics
   - A. Legal trade
   - B. Illicit traffic

III. Drug addiction

IV. Control
   - A. General
   - B. Systematic account of the work of the international bodies dealing with narcotics
   - C. Preparation of the new convention

I. RAW MATERIALS AND DERIVATIVES

A. OPIUM AND DERIVATIVES

E/CN.7/117	Methods of determining the origin of opium by chemical and physical means	14 April 1948
E/CN.7/117/Add.1 and Add.2	Examination of opium for distinguishing characteristics—some tentative methods	22 September 1948
E/CN.7/154	The problem of morphine synthesis	17 February 1949
E/CN.7/159	Methods of determining the origin of opium by chemical and physical means	15 April 1949
E/CN.7/159/Add.1	Ditto	9 May 1949
E/CN.7/159/Add.2	Ditto	31 May 1949
E/CN.7/W.54	Alkaloid industry in India	23 May 1949
E/CN.7/195	Methods of determining the origin of opium by chemical and physical means	26 March 1950
E/CN.7/202	Methods of determining the origin of opium by chemical and physical means	18 September 1950
E/CN.7/207	Ditto	19 October 1950
ST/SOA/SER.K/1	The assay, characteristics, composition, and origin of opium (No. 1: The determination of morphine in opium by extraction: A new method)	25 January 1951
ST/SOA/SER.K/2	The assay, characteristics, composition, and origin of opium (No. 2: The forms of crystals in Turkish opium, by Alâeddin Akçasu, Stambul, Turkey)	11 June 1951
ST/SOA/SER.K/3	The assay, characteristics, composition, and origin of opium (No. 3: The determination of morphine in raw opium, by Erich Knaffl-Lenz. Vienna, Austria)	1 August 1951
ST/SOA/SER.K/4	The assay, characteristics, composition, and origin of opium (No. 4: "Porphyroxine-Meconidine" in relation to the origin of opium (United Nations Secretariat))	11 September 1951
ST/SAO/SER.K/5	The assay, characteristics, composition, and origin of opium (No. 5: The ratio of narcotine to Meconic Acid in relation to the origin of opium (preliminary report from the government laboratory, London, England))	24 September 1951

ST/SOA/SER.K/6	The assay, characteristics, composition, and origin of opium (No. 6: The determination of Narcotine and Meconic Acid in opium. Second method (a report from the government laboratory, London, England) by J. R. Nicholls and E. G. Kellett)	24 September 1951
ST/SOA/SER.K/7	The assay, characteristics, composition, and origin of opium (No. 7: The determination of Narcotine and Meconic Acid in opium. Third method (a report from the government laboratory, London, England) by J. R. Nicholls and E. G. Kellett)	24 September 1951
ST/SOA/SER.K/8	The assay, characteristics, composition, and origin of opium (No. 8: Codeine and codeine-porphyroxine charts in relation to the origin of opium (United Nations Secretariat))	11 February 1952
ST/SOA/SER.K/9	The assay, characteristics, composition, and origin of opium (No. 9: Elimination of the other opium alkaloids in the assay of opium for morphine (United Nations Secretariat))	9 June 1952
ST/SOA/SER.K/10	The assay, characteristics, composition, and origin of opium (No. 10: The colorimetric determination of "Porphyroxine-meconidine". Communication on experiments to find a relation between "Red Lovibond Units" and absorption intensity value of the res "porphyr" solution, by Dr. L. Fuchs and Mr. W. Ullrich, University of Vienna, Austria)	25 September 1952
ST/SOA/SER.K/11	The assay, characteristics, composition, and origin of opium (No. 11: Assay of raw opium for morphine. A study of the method of Professor Erich Knaffl-Lenz. Laboratories of the S.E.M.P.A. Company, Paris)	2 October 1952
ST/SOA/SER.K/12	The assay, characteristics, composition, and origin of opium (No. 12: Determination of other titratable alkaloids in the morphine of opium assays (United Nations Secretariat))	14 October 1952

B. COCA LEAF AND DERIVATIVES

E/CN.7/73	Questionnaire on the limitation and the control of the cultivation and harvesting of the coca leaf	7 July 1947
E/CN.7/96	Request by the Government of Peru for a field survey of the effects of chewing of the coca leaf	4 August 1947
E/CN.7/105	Questionnaire on the limitation and the control of the cultivation and harvesting of the coca leaf	13 November 1947
E/CN.7/110	Replies from governments to the Questionnaire on the limitation and the control of the cultivation and harvesting of the coca leaf	19 April 1948
E/CN.7/110/Add.1	Ditto	21 April 1948
E/CN.7/110/Add.2	Ditto	30 April 1948
E/CN.7/110/Add.3	Ditto	25 June 1948
E/CN.7/110/Add.5	Ditto	6 April 1949
E/CN.7/W.34	Study on coca leaves	1 May 1948
E/CN.7/W.34	Ditto	14 June 1948
E/CN.7/112	General considerations for a plan for the limitation of the production of coca leaves	12 May 1948
E/CN.7/164	Commission of inquiry into the effects of chewing the coca leaf	20 April 1949
E/CN.7/164/Add.1	Ditto	9 May 1949
E/CN.7/164/Add.2	Ditto	14 May 1949
E/CN.7/164/Add.3	Ditto	27 May 1949
E/CN.7/164/Add.4	Ditto	31 May 1949
E/1666	The report of the United Nations Commission of Enquiry on the coca leaf	May 1950
E/CN.7/SR.118 E/CN.7/SR.119	Summary records of the 118th and 119th meetings of the Commission on Narcotic Drugs	
E/1666/Add.1 E/1666/Add.1/Rev.1	Report of the Commission of Enquiry on the Coca Leaf (Comments by members of the Commission on the statements of the representatives of Peru and Bolivia at the fifth session of the Commission on Narcotic Drugs)	8 June 1951
E/1666/Add.3	Report of the Commission of Enquiry on the coca leaf (statement circulated by the representative of Peru)	27 June 1951
E/CN.7/235	Report of the United Nations Commission of Enquiry on the coca leaf (communications from the Governments of Peru and Bolivia)	28 February 1952

C. INDIAN HEMP AND DERIVATIVES

E/CN.7/W.37	Study on cannabis sativa or hemp	11 May 1948
E/CN.7/113	Indian hemp	17 May 1948

II. TRADE IN NARCOTICS

A. LEGAL TRADE

E/CN.7/123	Estimates of world requirements of raw opium for medical and scientific purposes	3 May 1948
E/CN 7/123/Corr.1	Ditto	26 July 1948
E/CN.7/187	Export of opium from Iran to Indochina	6 July 1949
E/CN.7/197	Exports of raw opium by the producing countries during the period 1934-1948	20 June 1950
E/CN.7/W.4	Limitation of production of raw materials (table of the production, use, export and stocks of opium)	9 July 1947
E/CN.7/W.4/Add.1	Ditto	23 July 1947
E/CN.7/107	Limitation of the production of raw materials	6 April 1948
E/CN.7/107/Add.1	Ditto (poppy straw used in manufacture of morphine and other opium alkaloids, 1937-1946)	15 April 1948
E/CN.7/107/Add.2	Ditto	29 April 1948
E/CN.7/107/Add.3	Ditto	1 May 1948
E/CN.7/107/Add.4	Ditto	9 July 1948
E/CN.7/107/Add.5	Ditto	9 March 1949
E/CN.7/107/Add.6	Ditto	10 May 1949
E/C.S.7/8	Limitation of the production of raw materials (opium and coca leaf) used in the manufacture of narcotic drugs)	26 November 1946
E/C.S.7/6	Limitation of the production of raw materials (opium and coca leaf) used in the manufacture of narcotic drugs	26 November 1946

B. ILLICIT TRAFFIC

	A two-monthly summary of illicit transactions and seizures, reported by Governments under article 23 of the 1931 Convention, is published in the document series E/NS.19../Summary 1-6	
E/C.S.7/9	World trends of the illicit traffic in narcotic drugs during the war 1939-1945	23 November 1946
E/C.S.7/10	Review of the illicit traffic in narcotic drugs throughout the world during the years 1940 to 1945 and the first half of 1946	25 November 1946
E/C.S.7/15	The opium traffic in the United Kingdom 1931-1945	28 November 1946
E/C.S.7/48	Report of the Special Committee charged with the study of the question of the control of narcotic drugs in Japan and Korea	9 December 1946
E/C.S.7/60	Narcotic situation in Japan, Korea and the United States Zone in Germany	20 December 1946
E/CN.7/W.2	Annual reports for 1946, chapter V, Illicit traffic	24 June 1947
E/CN.7/W.3	Summary of illicit transactions and seizures	3 July 1947
E/CN.7/W.6	Control of narcotics in Japan	15 July 1947
E/CN.7/W.7	Summary of illicit transactions and seizures	18 July 1947
E/CN.7/W.10	Illicit traffic (methods of smuggling used by the traffickers)	21 July 1947
E/CN.7/W.12	The illicit traffic in Indian hemp in Great Britain since the war	21 July 1947
E/CN.7/W.15	Trends of illicit traffic during 1946	21 July 1947
E/CN.7/W.16	Convictions in respect of narcotic violations in Japan	21 July 1947
E/CN.7/W.19	Control of narcotics in Germany	29 July 1947
E/CN.7/W.20	Control of narcotics in Japan	11 August 1947
E/CN.7/W.22	Report by the opium suppression commission of the Chinese National Government on the discovery and taking into custody by the Shanghai maritime customs of narcotic drugs purchased by Powell and Sons, Ltd., from the United States Liquidation Commission	5 February 1948
E/CN.7/W.29	Summary of illicit transactions and seizures	14 April 1948
E/CN.7/W.30	Illicit traffic, chapter V of the annual reports	20 April 1948
E/CN.7/W.30/Add.1	Ditto	28 April 1948
E/CN.7/W.30/Add.2	Ditto	30 April 1948
E/CN.7/W.30/Add.3	Ditto	30 April 1948

E/CN.7/W.31	Memorandum on the illicit traffic in narcotic drugs during 1947	29 April 1948
E/CN.7/W.32	Information extracted from seizure reports received by the Secretariat between 1 March and 23 April 1948	30 April 1948
E/CN.7/W.33	Reports of governments on illicit traffic and the exchange of information under article 23 of the Limitation Convention of 1931	30 April 1948
E/CN.7/W.35	Summarized report of the Government of the Netherlands Indies for the period 1941-1947	4 May 1948
E/CN.7/W.42	Annual reports for 1948, chapter V, illicit traffic in Germany (A. British Zone of Occupation; B. United States Zone of Occupation)	5 April 1949
E/CN.7/W.42/Add.1	Ditto	15 April 1949
E/CN.7/W.42/Add.1/Corr.1	Ditto	9 May 1949
E/CN.7/W.42/Add.2	Ditto	30 April 1949
E/CN.7/W.42/Add.3	Ditto	12 May 1949
E/CN.7/W.46	Information extracted from seizure reports received by the Secretariat between 1 March and 30 April 1949	4 May 1949
E/CN.7/W.47	Memorandum on the illicit traffic in narcotic drugs during 1948	6 May 1949
E/CN.7/153	Illicit traffic in Germany	18 January 1949
E/CN.7/153/Add.1	Ditto	
E/CN.7/170	Decree-laws enacted by the Peruvian Government to combat the illicit traffic in narcotic drugs	13 May 1949
E/CN.7/206	Control of the illicit traffic in narcotics in Germany	21 November 1950
E/CN.7/206/Corr.1	Ditto	27 November 1950
E/CN.7/212	Memorandum on the illicit traffic in narcotic drugs during 1949	30 November 1950
E/CN.7/213	Review of the illicit traffic in narcotic drugs throughout the world during the year 1949 and the first nine months of 1950	17 November 1950
E/CN.7/217	Illicit traffic: situation in Germany	8 December 1950
E/CN.7/222	Illicit traffic	4 April 1951
E/CN.7/222/Corr.1	Ditto (seizures of opium in Thailand)	18 April 1951
E/CN.7/223	Annual reports by governments for 1950, chapter V, illicit traffic	10 April 1951
E/CN.7/226	Illicit traffic in 1949 and 1950	11 April 1951
E/CN.7/224	Memorandum on the illicit traffic in narcotic drugs during 1950	16 April 1951
E/CN.7/232	Chapter V of the annual reports by governments for 1951 under the 1931 Convention	18 March 1952
E/CN.7/232/Add.1	Ditto	4 April 1952
E/CN.7/232/Add.2	Ditto	7 April 1952
E/CN.7/232/Add.3	Ditto	14 April 1952
E/CN.7/232/Add.4	Ditto	24 April 1952
E/CN.7/234	Memorandum by the Secretary-General on the illicit traffic in narcotic drugs during 1951	17 April 1952
E/CN.7/236	Memorandum by the International Criminal Police Commission on Illicit Traffic in Narcotic Drugs in 1951	25 March 1952
E/CN.7/237	Illicit traffic in diacetylmorphine	3 April 1952
E/CN.7/238	A report by the Director of the Arab League Permanent Anti-Narcotics Bureau together with a supplementary note	22 April 1952

III. DRUG ADDICTION

E/C.S.7/26	Drug addiction	2 December 1946
E/CN.7/64	Questionnaire regarding legal and practical standpoint taken up regarding drug addiction and drug addicts	11 April 1947
E/CN.7/111	Replies from governments to the Questionnaire regarding legal and practical standpoint taken up regarding drug addiction and drug addicts	17 May 1948
E/CN.7/111/Add.1	Ditto	4 May 1948
E/CN.7/111/Add.2	Ditto	9 March 1949
E/CN.7/111/Add.3	Ditto	22 April 1949
E/CN.7/111/Add.4	Ditto	6 April 1949

E/CN.7/166	Classification and analysis of replies from governments to the questionnaire regarding the legal and practical standpoint taken up regarding drug addiction and drug addicts (E/CN.7/64, E/CN.7/111 and E/CN.7/111/Add.1)	30 April 1949
E/CN.7/189	Drug addiction (replies to the Questionnaire on drug addiction (Japan))	2 February 1950

IV. CONTROL

A. GENERAL

E/NAR/1	Transfer to the United Nations of powers exercised by the League of Nations under the conventions on narcotic drugs	31 July 1946
E/NT/1	First Opium Conference: Agreement, Protocol, Final Act signed at Geneva, 11 February 1925, and amended by the Protocol signed at Lake Success, New York, 11 December 1946	
E/NT/2	Second Opium Conference: Convention, Protocol, Final Act Amended by the Protocol signed at Lake Success, New York, 11 December 1946	
E/NT/3	Conference for the Limitation of the Manufacture of Narcotic Drugs, Geneva, 27 May-13 July 1931: Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, Protocol of Signature and Final Act: amended by the Protocol signed at Lake Success, New York, 11 December 1946	
E/NT/4	Conference on the Suppression of Opium-Smoking convened under article XII of the Geneva Opium Agreement: Agreement and Final Act signed at Bangkok, 27 November 1931, and amended by the Protocol signed at Lake Success, New York, 11 December 1946	
E/NT/5	Conference for the Suppression of the Illicit Traffic in Dangerous Drugs: Convention of 1936 for the Suppression of the Illicit Traffic in Dangerous Drugs, Protocol of Signature and Final Act signed at Geneva 26 June 1936 and amended by the Protocol signed at Lake Success, New York, 11 December 1946	
E/NT/6	Protocol on Narcotic Drugs: Protocol amending the Agreements, Conventions and Protocols on Narcotic Drugs concluded at The Hague on 23 January 1912, at Geneva on 11 February 1925 and 19 February 1925 and 13 July 1931, at Bangkok on 27 November 1931 and at Geneva on 26 June 1936	
E/NT/7	Protocol bringing under international control drugs outside the scope of the Convention of 13 July 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, as amended by the Protocol signed at Lake Success on 11 December 1946	
E/C.S.7/5	Convention for limiting the Manufacture and Regulating the Distribution of Narcotic Drugs of 13 July 1931: list of firms authorized to manufacture drugs covered by the convention	23 November 1946
E/C.S.7/11	Statement of ratifications or definite adhesions to the international conventions and agreements on narcotic drugs	27 November 1946
E/C.S.7/7	Abolition of opium-smoking in the Far East	27 November 1946
E/C.S.7/38	Re-establishment at its pre-war level of international control of narcotic drugs	5 December 1946
E/C.S.7/03	Limitation of production of raw materials (questionnaire on the limitation and control of the cultivation of the opium poppy and the production of raw opium)	
E/CN.7/69	*Notes verbales* despatched to implement resolutions concerning narcotic drugs	19 May 1947
E/CN.7/74	Abolition of opium-smoking in the Far East	9 July 1947
E/CN.7/W.5	General survey of the situation in regard to the fulfilment by governments of their obligation under article 21 of the 1931 Convention to "Forward to the Secretary-General an Annual Report on the working of the Convention in their Territories"	14 July 1947
E/CN.7/80	Study of measures to be taken with a view to bringing under international control narcotic drugs not covered by conventions at present in force	18 July 1947
E/CN.7/80/Rev.1	Decisions taken by the Commission on Narcotic Drugs at a meeting held on 25 July 1947	26 July 1947
E/CN.7/80/Rev.2		2 August 1947
E/CN.7/101	Commission on Narcotic Drugs: amendment of article 19 of the 1925 Convention	5 August 1947

E/CN.7/W.23	Extracts from the report presented to Congress by the Minister of Health. 1947 [of Colombia]	1 March 1948
E/CN.7/107	Limitation of production of raw materials: replies to the questionnaire on raw opium, addenda 1-6	6 April 1948
E/CN.7/108	Limitation of the production of raw materials	3 May 1948
E/CN.7/108/Corr.1	Analytical summary of the replies from governments to the questionnaire on raw opium	12 May 1948
E/CN.7/115	Draft protocol to bring under international control certain drugs not covered by the 1931 Convention	12 April 1948
E/CN.7/115/Add.1	Answer of the Indian Government to the Draft Protocol	26 April 1948
E/CN.7/115/Add.2	Answer of the Government of Egypt to the Draft Protocol	29 April 1948
E/CN.7/120	*Notes verbales* dispatched to governments by the Secretary-General to implement decisions adopted by the Commission and the Economic and Social Council or in execution of the provisions of the conventions on narcotic drugs	16 April 1948
E/CN.7/121	Application of article 15 of the 1931 Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs as amended by the Protocol of 11 December 1946 (special national administrations)	25 April 1948
E/CN.7/W.36	Limitation of the production of raw materials. Opium producing areas of the world and kinds of opium, monograph, by Charles C. Fulton	5 May 1948
E/CN.7/W.39	Report to the Economic and Social Council on the Draft Protocol to Bring under Control Certain Drugs not Covered by the 1931 Convention	17 May 1948
E/CN.7/165	Abolition of opium-smoking in the Far East	7 April 1949
E/CN.7/165/Add.1	Answers of Hungary and the United Kingdom (for Hong Kong)	6 May 1949
E/CN.7/165/Add.2	Reply of the French Government regarding Indochina	23 May 1949
E/CN.7/165/Add.3	Answer of the United Kingdom for Singapore	20 May 1949
E/CN.7/165/Add.4	Further replies	12 July 1949
E/CN.7/W.45	The placing of acetyldihydrocodeine under international control	22 April 1949
E/CN.7/157	Circular communications dispatched by the Secretary-General in connexion with decisions taken by the Commission on Narcotic Drugs and resolutions adopted by the Economic and Social Council, or in execution of provisions of the conventions on narcotic drugs	5 May 1949
E/CN.7/158	Application of article 15 of the 1931 Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs as amended by the Protocol of 11 December 1946 (special national administrations)	12 April 1949
E/CN.7/W.55	Abolition of opium-smoking in the Far East	24 May 1949
E/NF.1950/1	Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs of 13 July 1931 (list of firms authorized to manufacture drugs covered by the Convention)	8 February 1950
E/1632	Question of the exemption of ipecopan from the provisions of the internatonal conventions on narcotic drugs	23 February 1950
E/CN.7/190	Limitation of production of raw materials (reply to the questionnaire on raw opium (India))	6 February 1950
E/CN.7/193	Abolition of opium-smoking in the Far East	26 April 1950
E/CN.7/209	Notifications by the Governments of Turkey and the United States of America under article 1, paragraph 1, of the Protocol of 19 November 1948 bringing under international control drugs outside the scope of the Convention of 13 July 1931 for limiting the manufacture and regulating the distribution of narcotic drugs, as amended by the Protocol of 11 December 1946	17 November 1950
E/CN.7/229	Abolition of opium-smoking in the Far East	11 January 1952
E/CN.7/229/Add.1	Ditto	9 April 1952
E/CN.7/229/Rev.1	Ditto	21 March 1952
E/CN.7/229/Add.2	Ditto	28 April 1952
E/CN.7/239	Co-operation between the United Nations and the Universal Postal Union in the international control of narcotic drugs	21 April 1952
E/NR.19../..	Under article 21 of the 1931 Convention, governments are bound to furnish annual reports covering their work in the field of narcotics. The Secretariat receives approximately 120 such reports every year	
E/NR.19../Summary	A summary of the annual reports covering each calendar year is published by the Secretariat	

E/CN.7/W.13	Annual reports of governments for 1944	21 July 1947
E/CN.7/W.14	Annual reports of governments for 1945	21 July 1947
E/CN.7/W.26	Annual reports of governments for 1946	5 April 1948
E/CN.7/W.43	Annual reports of governments for 1947	15 April 1949
E/CN.7/78	Commission on Narcotic Drugs: Laws and Regulations	12 July 1947
E/NL.19../..	Under the article 21 of the 1931 Convention, governments are bound to furnish the laws and regulations dealing with narcotics promulgated during each year. Between 100 and 120 such laws are received annually	
E/NL.19../Summary	A summary of these laws is issued yearly[1]	
E/NA.1947/1 E/NA.1949/1 E/NA.1950/1 and Corr.1 to 18	Geneva Convention of 1925 and the Convention of 1931 for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, as amended by the Protocol of 11 December 1946: the system of import certificates and export authorizations: a list of names and addresses of national authorities	

B. SYSTEMATIC ACCOUNT OF THE WORK OF THE INTERNATIONAL BODIES DEALING WITH NARCOTIC DRUGS

1. Commission on Narcotic Drugs

E/C.S.7/4	Commission on Narcotic Drugs: Terms of reference	18 November 1946
E/CN.7/75	Commission on Narcotic Drugs: Revised minutes of the first session	14 July 1947
E/CN.7/106	Commission on Narcotic Drugs: Summary records of the second session	7 January 1948
E/CN.7/122	Renewal of the membership of the Commission—measures to be taken to ensure the continuity of its functions	28 April 1948
	Commission on Narcotic Drugs: Report of the first session	27 November 1946 13 December 1946
E/575 E/575/Add.1 E/575/Add.2	Commission on Narcotic Drugs: Report of the second session	12 September 1947 5 February 1948 20 February 1948
E/CN.7/W.40	Report to the Economic and Social Council on the third session of the Commission	20 May 1948
E/1361 E/CN.7/186	Report of the fourth session of the Commission on Narcotic Drugs	7 June 1949
E/1361/Add.1	(Financial estimate prepared in accordance with rule 33 of the rules of procedure of the Economic and Social Council)	10 June 1949
E/1361/Add.2	Addendum from China	6 July 1949
E/1889	Commission on Narcotic Drugs: Report of the fifth session	29 December 1950
E/1889/Rev.1 E/CN.7/216/Rev.1	Commission on Narcotic Drugs: Report of the fifth session	29 December 1950
E/1998 E/CN.7/227	Commission on Narcotic Drugs: Report of the sixth session	1 June 1951
E/1998 E/CN.7/227/Rev.1	Commission on Narcotic Drugs: Report of the sixth session	1 June 1951
E/2219 E/CN.7/240	Commission on Narcotic Drugs: Report of the seventh session	15 May 1952
E/CN.7/82	Progress report to the second session	23 July 1947
E/CN.7/125	Progress report to the third session	30 April 1948
E/CN.7/125/Add.1	Ditto	30 April 1948
E/CN.7/160	Progress report to the fourth session	13 May 1949
E/CN.7/160/Add.1	Ditto	5 May 1949
E/CN.7/196	Progress report to the fifth session	21 June 1950
E/CN.7/225	Progress report to the sixth session	9 April 1951
E/CN.7/231	Progress report to the seventh session	3 March 1952
E/CN.7/231/Add.1	Ditto	8 April 1952

2. Permanent Central Opium Board

E/OB/1	Permanent Central Opium Board: Report on the work of the Board	21 October 1946
E/OB/2	Permanent Central Opium Board: Report on the work of the Board	November 1947

[1] The first was published with the symbol E/CN.7/118, April 1948, addendum, May 1948.

E/OB/4	Permanent Central Opium Board: Report to the Economic and Social Council on statistics of narcotics for 1947 and the work of the Board in 1948	December 1948
E/OB/5 Addendum	Permanent Central Opium Board: Report to the Economic and Social Council on statistics for 1948 and the work of the Board in 1949	December 1949
E/OB/6	Permanent Central Opium Board: Report to the Economic and Social Council on statistics of narcotics for 1949 and the work of the Board in 1950	November 1950
E/OB/7 Addendum	Permanent Central Opium Board: Addendum to the report to the Economic and Social Council on statistics of narcotics for 1950 and the work of the Board in 1951	December 1951
E/OB/8	Permanent Central Opium Board: Report to the Economic and Social Council on statistics of narcotics for 1951 and the work of the Board in 1952	November 1952

3. Drug Supervisory Body

E/DSB/3	Drug Supervisory Body: Estimated world requirements of dangerous drugs in 1947	
E/DSB/4	Drug Supervisory Body: Estimated world requirements of narcotic drugs in 1948	December 1947
E/DSB/6	Drug Supervisory Body: Estimated world requirements of narcotic drugs in 1949	December 1948
E/DSB/7	Drug Supervisory Body: Estimated world requirements of narcotic drugs in 1950	December 1949
E/DSB/8	Drug Supervisory Body: Estimated world requirements of narcotic drugs in 1951	December 1950
E/DSB/9	Drug Supervisory Body: Estimated world requirements of narcotic drugs in 1952	15 December 1951
E/DSB/10	Drug Supervisory Body: Estimated world requirements of narcotic drugs in 1953	15 December 1952

4. Resolutions of the Economic and Social Council

	First and second sessions: See Journal of the Economic and Social Council	
E/245/Rev.1	Third session	3 May 1947
E/437	Fourth session	22 May 1947
E/573	Fifth session	2 September 1947
E/777	Sixth session	12 March 1948
E/1065	Seventh session	30 August 1948
E/1310	Eighth session	15 March 1949
E/1553	Ninth session	15 August 1949
E/1661	Tenth session	19 April 1950
E/1849	Eleventh session	31 August 1950
E/1987	Twelfth session	3 May 1951
E/2152	Thirteenth session	10 October 1951
E/2332	Fourteenth session	13 August 1952

C. PREPARATION OF THE NEW CONVENTION

E/CN.7/63	Preparatory work with a view to the holding of an international conference to consider the possibility of limiting and controlling the cultivation of the opium poppy and the production of raw opium and controlling other raw materials used in the manufacture of opium alkaloids	26 February 1947
E/CN.7/W.41	Unification of conventions on narcotic drugs	31 March 1949
E/CN.7/W.44	Unification of conventions on narcotic drugs. The international control authority	13 April 1949
E/CN.7/W.44/Corr.1	Ditto	22 April 1949
E/CN.7/W.53	Unification of conventions on narcotic drugs control of international trade	4 May 1949
E/CN.7/W.52	Memorandum on the desirability of convening a conference for the purpose of reaching an interim agreement limiting the production and export of opium to medical and scientific needs	12 May 1949

E/CN.7/W.50	Unification of conventions on narcotic drugs. Outline of general principles on which a new single convention might be based	24 May 1949
E/CN.7/188	Report of the *Ad-hoc* Committee of the Principal Opium-Producing Countries	9 January 1950
E/CN.7/AC.3/2	Preparatory documentation on the single convention	February 1950
E/CN.7/AC.3/1	Preparatory documentation on the single convention	February 1950
E/CN.7/AC.3/4	Commentary on the draft single convention	March 1950
E/CN.7/AC.3/4/Rev.1	Ditto	26 October 1950
E/CN.7/191	Summary records of the *Ad-hoc* Committee of the Principal Opium-Producing Countries	17 March 1950
E/CN.7/AC.3/R.1	Committee on a Single Convention on Narcotic Drugs. Preparatory documentation	25 April 1950
E/CN.7/194	Proposed interim opium agreement international opium monopoly	26 April 1950
E/CN.7/198	Proposed interim opium agreement	27 June 1950
E/CN.7/199	Draft of the proposed interim agreement to limit the production of opium to medical and scientific needs	13 July 1950
E/CN.7/199/Rev.1	Ditto	31 October 1950
E/CN.7/200	Report of the meeting of representatives of the principal drug-manufacturing countries	1 September1950
E/CN.7/201	Report of the joint Committee of the Principal Drug-Producing Countries and of the Principal Drug-Manufacturing Countries on its first session	1 September 1950
E/CN.7/203	Consolidated summary record of the meeting of representatives of the principal drug-manufacturing countries	18 October 1950
E/CN.7/204	Consolidated summary records of the joint Committee of the Principal Opium-Producing Countries and of the Principal Drug-Manufacturing Countries	3 November 1950
E/CN.7/214	Report of the joint Committee of the Principal Opium-Producing Countries and of the Principal Drug-Manufacturing Countries on the second part of the first session	1 December 1950
E/CN.7/214/Corr.1	Ditto	6 December 1950
E/CN.7/215	Consolidated summary record of the second part of the first session of the joint Committee of the Principal Opium-Producing Countries and of the Principal Drug-Manufacturing Countries held at United Nations Headquarters from Tuesday, 14 November to Thursday, 30 November 1950	13 December 1950
E/CN.7/221	Draft of the proposed interim agreement to limit the production of opium to medical and scientific needs	6 April 1951
E/CN.7/AC.3/3	Draft of the single convention	October 1951
E/CN.7/AC.3/5	An annotated compilation of observations on the draft of the single convention	3 March 1952

ERRATA

Corrections to *Bulletin on Narcotics*, volume IV, No. 4

Page 3, paragraph 3: instead of "a person chronically infected with morphine feels no further desire...", read: "a person not chronically infected with morphine feels no further desire...".

Page 11, last paragraph of first column: instead of "dihydrooxymorphine-D...", read: "dihydrodesoxymorphine-D...".

Page 23, footnote, second line: instead of "The reagent platinic chloride in 1N HCl is prepared...", read: "The reagent platinic iodide in dilute HCl is prepared...".

Page 23, footnote, fourth line: instead of "diluted with 45 ml. 90.1 per cent KI solution...", read: "diluted with 45 ml. of 0.1 per cent KI solution...".

Page 31, third paragraph under "Marquis' reagent": instead of "phenol-etrahydrocannabinol...", read: "phenol tetrahydrocannabinol...".

Page 31, second paragraph under "Wasicky's reagent": should have a semicolon following "authors".

Page 31, third paragraph: instead of "phenol and resorcin pyragallol", read: "phenol, resorcin, and pyrogallol...".

Page 31, second paragraph under "Froehde's reagent" (second column): omit "fading".

Page 31, third paragraph under "Froehde's reagent" (second column): "mg" should be changed to "g" throughout except for the parenthetical "(1 mg./ml.)".

In the second line of this paragraph "100 ml. of" should be inserted before "concentrated" and in the fourth line, instead of "a definite variation", read: "the definite variation".